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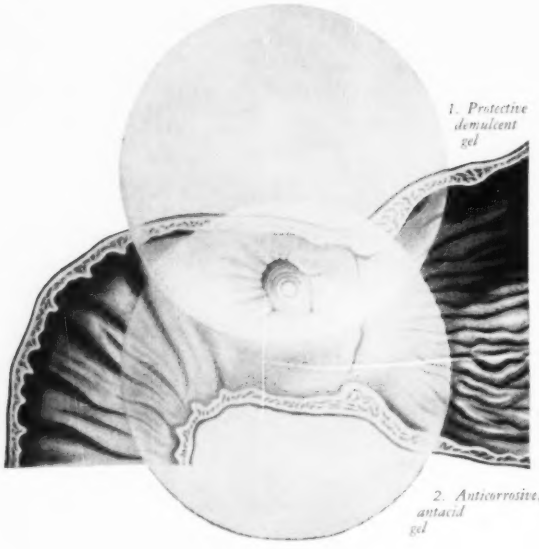

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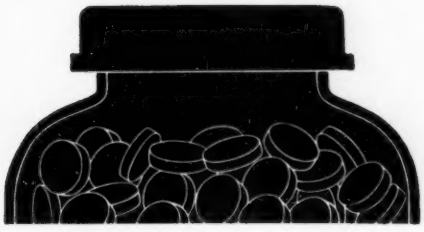

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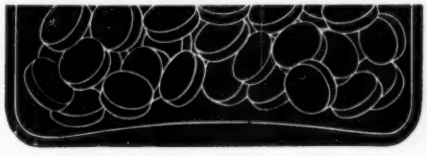

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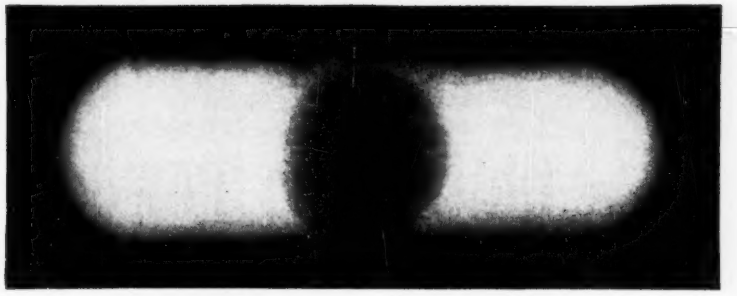

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1. Offenkrantz, W. F., *Rev. Gastroenterol*, 17:359-367 (May), 1950.

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(1) Thorn, G.W., Quimby, J.T., and Marshall, C., Jr., Ann. Int. Med. 18:913 (June) 1943.
(2) Orent-Keiles, E., and Hallman, L. F., Circular No. 827, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, Dec., 1949.

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THE GASTROINTESTINAL SYNDROME OF CHRONIC BRUCELLOSIS

HARRY GAUSS, M. D., Denver, Colorado.

BRUCELLOSIS is commonly considered to be an infection, acute or chronic in character, caused by the brucella group of micro-organisms and characterized by fever, weakness, sweating and muscular aches.

Brucellosis happens to be endemic in Colorado as well as in other parts of the world, hence our attention has been focused on this disease for some time, and we have come to realize that this disease does not always conform to any set pattern, but has many clinical expressions including a strong gastrointestinal syndrome which may at times completely dominate the clinical picture, particularly in the chronic state.

On numerous occasions we have struggled with a refractory gastrointestinal syndrome suggestive of a functional disorder but which would not respond to the usual therapeutic methods, and which by the process of trial and error in differential diagnosis turned out to be a case of brucellosis.

We have come to regard brucellosis as a disease of many manifestations. Like syphilis it may masquerade as other diseases, and one of these is functional disorders of the gastrointestinal tract.

The diagnosis of chronic brucellosis at times is an involved process. Sometimes its presence is suggested by the history of the patient, which on careful interrogation brings forth the information that the patient may have consumed unpasteurized milk any time within the preceding several years. Sometimes it is suggested by the occupation of the patient, because there are certain groups of persons who are predisposed to the disease by reason of their occupations such as farmers and ranchers who handle cattle, sheep, goats and pigs and frequently assume the duties of midwives to their animal charges in the performance of their routine chores. Likewise veterinarians are exposed to infection by reason of their direct contact with infected animals, so are slaughter house employees as well as numerous others.

In Colorado many persons are or have been exposed to the danger of consuming unpasteurized milk. Colorado has had a state pasteurization law in effect only since June 1, 1949, although some of the larger cities have required pasteurization of city sold milk for longer periods of time. Denver has had a city pasteurization law since 1943. Nevertheless much of Colorado's population including the urban population is still exposed to brucellosis even today, since much of Colorado's urban population spends its week-ends in the hills, eats in all manner of out-of-the-way resorts where pasteurization is difficult to enforce. Furthermore Colorado still has a large rural population who are regularly visited by their city cousins, and many of the rural cousins are not convinced of the need of pasteurization. All of which means that a large part of Colorado's population including the urban portion are exposed to the danger of infection from brucellosis because of their contacts with the rural and out-of-the-way eating houses where it is difficult to enforce pasteurization.

Submitted Jan. 30, 1950.
Department of Medicine, University of Colorado.

Most of the cases of chronic masked brucellosis that we have encountered have been picked up in our private practice where we have been looking for them in certain groups of patients where experience has taught us that they are likely to occur. These groups of potential cases are: (1) those who are exposed to infection by reason of having consumed raw milk, as farmers, ranchers, inhabitants and visitors to rural areas; certain persons in urban areas who keep cows and goats for their own convenience, etc. Thus one family living at the edge of Denver kept a milch cow. All four members of this family were found to be infected. A coal miner living in the hills kept a goat for milk purposes. Two of his family were found to be infected. A Denver newspaper woman had a mountain cabin and purchased milk from a local rancher; she was found to be infected. A Denver manufacturer of machinery visited a rancher to sell him some equipment and stopped for lunch. He returned with a large order in his pocket and brucellosis in his system. A Denver college professor went pheasant shooting on a friend's ranch and ate his supper there; he returned with the legal limit of three cock pheasants in his bag besides the brucellosis in his system; and so it goes. (2) Certain patients with functional disorders of the gastrointestinal tract who prove refractory to treatment and do not give the anticipated response. (3) The "psycho" group including those diagnosed as psychoneurosis and neurasthenia, and others who go on complaining month after month and who do not make the expected progress. (4) Those who manifest minor elevations of temperature at times.

It is in these groups that we encounter most of the masked cases of brucellosis which present a gastrointestinal syndrome as the chief complaint. We are not including in this report the frank open cases of brucellosis with the established syndrome.

We have selected twenty case histories for discussion where the patient presented an essential gastrointestinal history as the chief complaint, but where the subsequent study revealed the presence of a masked chronic brucellosis.

The gastrointestinal symptoms seem to fall into four groups, (1) a predominant gastric irritation syndrome, (2) an irritable colon syndrome, (3) a biliary dyspepsia syndrome, (4) mixed syndrome.

THE GASTRIC IRRITATION SYNDROME

The gastrointestinal expression of chronic brucellosis sometimes suggests the gastric irritation syndrome. The patient usually complains of diffuse epigastric distress which occurs at odd times during the day. Sometimes it occurs at the end of the gastric cycle, sometimes shortly after eating. Some of the patients describe the distress as a sensation of rawness. This sensation of rawness is felt over most of the epigastrium; it is diffuse in distribution. It is not localized and does not have either the anatomic character or gastric cycle character of peptic ulcer pain. However we did encounter one patient who had a true bleeding duodenal ulcer.

SUMMARY OF TWENTY CASES OF CHRONIC BRUCELLOSIS PRESENTING A GASTROINTESTINAL SYNDROME

Case	Patient	Sex	Age	Gastrointestinal Syndrome	Other Symptoms	Skin Test	Treatment
1.	M.A.	F	40	Epigastric distress, rawness, diffuse abdominal distress, excessive belching, bloating after meals, constipation	Fatigue, delayed low grade fever	Positive	Aureomycin
2.	N.H.	F	60	Belching and bloating after meals, "Can't digest food," abdominal consciousness, regurgitation, loss of appetite	Dizziness, unsteady gait, fatigue, restlessness	Positive	Dihydrostreptomycin, sulfadiazine
3.	L.R.M.	F	29	Constipation, indigestion, abdominal consciousness, diffuse abdominal distress	Irritability, fatigue, irritable skin	Positive	Dihydrostreptomycin, sulfadiazine
4.	E.G.T.	F	60	Belching and bloating after meals, clay colored stools, intolerance for fried foods, onions, etc., epigastric fullness	Muscular tremors, dry throat, joint pains, fatigue	Positive	Aureomycin
5.	S.B.	F	31	Pain, right lower quadrant, gas, abdominal cramps, constipation, substernal pains, Acute Appendicitis	Palpitation, restlessness, tachycardia, anemia	Positive	Aureomycin
6.	W. A.	M	40	"Sick to stomach", nausea, abnormal appetite, epigastric distress	Headache, backache, dizziness, weakness	Positive	Aureomycin
7.	H.M.	M	33	Constipation, bloating, belching, intolerance for fried foods, onions, etc., clay colored stools	Insomnia, loss weight, 12 lbs., fatigue	Positive	Aureomycin
8.	M.J.	F	23	Diffuse, vague abdominal distress, constipation, gas distress	Loss of 15 lbs., fatigue, headaches, irritability	Positive	Aureomycin
9.	N.P.	F	23	Nausea, flatulence, bloating, upper abdominal fullness	Fatigue, dizziness, nervousness, headaches	Positive	Brucellin
10.	E.O.	M	54	Belching, bloating, epigastric distress, fullness after meals, distress R. U. Q., intolerance for fried foods, onions, etc., "foods do not digest," nausea	Joint pains, palpitation, giddiness, weakness	Positive	Aureomycin
11.	A.O.	M	39	Constipation, flatulence, unsatisfactory stools, vague abdominal distress	Fatigue, backache, muscular weakness	Positive	Aureomycin
12.	L.O.	M	44	Diffuse burning in abdomen, constipation, irritated bowel, flatulence, bloating	Joint pains, fatigue, weakness	Positive	Aureomycin
13.	J.M.G.	M	35	Epigastric distress, rawness in upper abdomen, acid eructations, food "sours"	Palpitation, giddiness, muscular tremors	Positive	Brucellin
14.	B.E.F.	F	57	Belching and bloating, epigastric fullness, constipation	Delayed low grade fever, dizziness	Positive	Dihydrostreptomycin, sulfadiazine
15.	C.G.	M	33	Loss of appetite, "sick to stomach", clay colored stools, bloating, intolerance for fried foods, onions, etc.	Headaches, insomnia, joint pains	Positive	Aureomycin
16.	M.J.G.	M	55	Intolerance for fried foods, onions, etc., clay colored stools, constipation, lower abdominal distress, belching and bloating	Joint pains, headaches, palpitation, weakness	Positive	Aureomycin
17.	D.B.	M	48	Flatulence, bloating, constipation, intolerance for fried foods, cabbage, onions, etc., clay colored stools	Weakness, irritability, headaches, fatigue	Positive	Aureomycin
18.	C.L.	M	37	Heartburn, epigastric distress acid eructations, fullness after meals, bleeding duodenal ulcer	Palpitation, weakness, joint pains	Positive	Dihydrostreptomycin, sulfadiazine
19.	M.R.T.	F	33	Heartburn, rawness in epigastrium, acid eructations, substernal distress, gas distress	Joint pains, weakness, backache, giddiness	Positive	Aureomycin
20.	W.G.	M	49	Nervous stomach, gas distress, constipation, diffuse abdominal distress, intolerance for fried foods, cabbage, etc.	Backache, muscular pains, palpitations, chest pains	Positive	Chloramphenicol

The feeling of rawness is located in most of the epigastrium and probably is a referred distress from the stomach. Its clinical character suggests the gastric distress observed in acoholic gastritis. The distress is relieved by warm milk, bland foods, aluminum hydroxide gel, other adsorbents. Frequently the distress is made worse by a heavy meal, also by acid foods, raw apples, coarse foods, iced foods and beverages. Some patients also describe a feeling of fullness after meals with a tendency towards belching. The appetite is poor. The patient has lost his zest for foods, and many have learned by their own experiences to seek relief from the distress by the ingestion of warm bland foods.

X-ray of the stomach usually shows a highly irritable stomach with increased peristaltic waves of greater frequency. The duodenal cap is usually irritable in the sense that it does not hold the barium meal well, but tends to evacuate it rapidly. The duodenal cap while irritable does not have the fixed filling defect pattern encountered in duodenal ulcer. We did observe one patient with a true duodenal ulcer. However this incidence is no greater than one might expect to find in the study of any group of patients of this size. The stomach usually empties in normal time, sometimes faster than normal, while sometimes there is a tendency towards pylorospasm.

We did not make gastroscopic studies on these patients.

The gastric expression of brucellosis is not surprising since the original description of the disease by Marston in 1861 designated it as "Mediterranean or gastric intermittent fever." Marston mentions subacute dyspepsia, anorexia, nausea, great derangement of the assimilative organs, tenderness in the epigastric region, etc. In 1937, Harris wrote on the difficulties encountered in the diagnosis of brucellosis. He mentions the occurrence of epigastric pain in some patients and a more or less typical ulcer syndrome which often occurs in brucellosis in the absence of actual ulcer as shown by operation and radiography.

Our own experience with a single instance of bleeding duodenal ulcer is regarded as a normal incidence of peptic ulcer in a group of this size and type.

With reference to the gastric symptoms, it is our impression that we are dealing with a true gastric irritation syndrome based on a mild toxic gastritis resulting from the infiltration of the gastric wall by the toxic products resulting from bacterial activity of the Brucella.

THE IRRITABLE COLON SYNDROME

The patient complains of constipation, the passage of small constricted stools, a feeling of diffuse abdominal distress which may involve much of the abdomen. Some of the patients describe the distress as a sensation of rawness, usually there is excessive flatulence, frequently headache is complained of, also coated tongue and diminished appetite. Abdominal consciousness is frequently mentioned and is described as a diffuse vague sort of distress which increases in some patients to a feeling of rawness. This distress is not localized but is usually diffuse in character and may involve any or all parts of the abdomen. The distress suggests that described by patients with mucous colitis, but the patient with brucellosis does not pass mucus in his stools. Another differential point from mucous colitis is that whereas in mucous colitis, the pain is apt to be localized in one of several areas in the abdomen, such as under the left costal margin or other areas, the abdominal distress of brucellosis suggesting the colon irritation is seldom localized, rather it is diffuse in character.

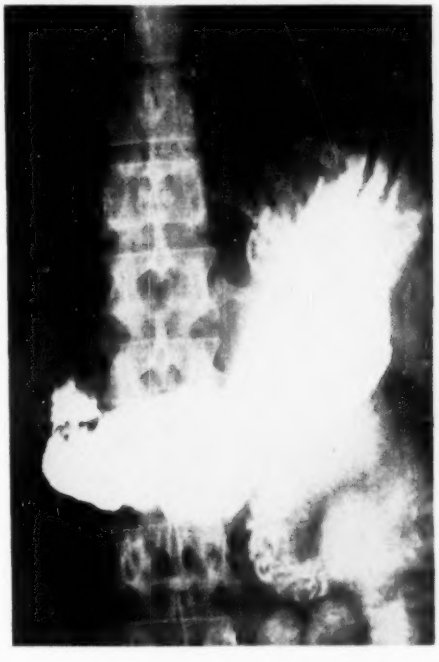
Constipation is common. The patient passes small infrequent stools which are of the pencil shape or contracted form. Sometimes headaches are present. These are dull in character, diffuse in their distribution, and may involve the frontal, parietal or occipital regions or all of them. The headache is seldom unilateral in its distribution, nor does it have a violent character of migraine. The headache usually suggests a toxic origin rather than a vascular one, as indeed it probably has.

Coated tongue is commonly present, also loss of appetite, also muscular fatigue, loss of energy, inability to concentrate, eye fatigue, general irritability and other symptoms commonly encountered in constipation.

X-ray studies usually show an irritable colon with reduced lumen. Spasticity of the colon occurs which may involve any segment of the colon. The barium meal travels rapidly and often evacuates at a faster rate than normal. The colon often assumes a stringy or ropy appearance of the type encountered in mucous colitis.

Harris mentions that brucellosis may simulate ulcerative colitis. Further he believes that appendicitis may also be simulated and he mentions eleven patients in whom appendectomy was performed.

Our own experience with a single case of acute appendicitis is not conclusive, although it does confirm his impressions.



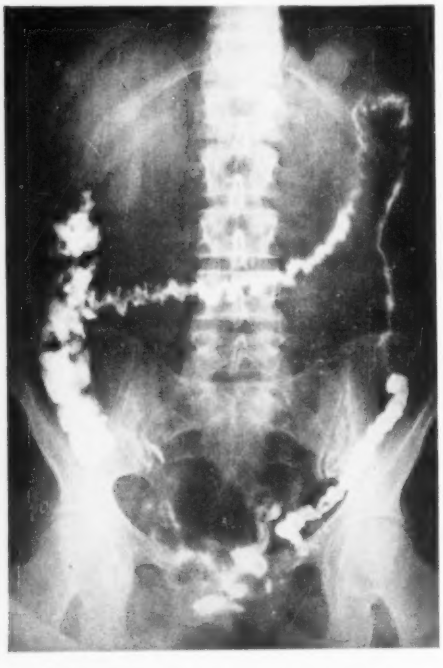
Stomach in a patient with clinical brucellosis who manifested the gastric irritation syndrome. The film shows an extremely irritable duodenal cap.

The irritable syndrome like the gastric irritation syndrome is probably toxic in origin and results from the infiltration of the intestinal wall by the products of bacterial activity resulting from the Brucella infection.

THE BILIARY DYPEPSIA SYNDROME

The gastrointestinal symptoms described by some patients strongly suggest the presence of a biliary dyspepsia and run the gamut from the characteristic food intolerances to the clay colored stools. Quite likely the underlying mechanism for this syndrome is a toxic and inflammatory involvement of the biliary system.

The patients in this group commonly describe a fullness after meals localized in the epigastrium, accompanied by a desire to belch which affords some relief temporarily. These patients do not tolerate those foods which are commonly mentioned by patients with the accepted syndrome of gall bladder dyspepsia. They include such items as fried foods, greasy foods, chocolate, onions, cabbage, cauliflower, radishes, and cucumbers, shell fish, etc. They experience a sensation of fullness and heaviness after a heavy meal and often feel the necessity of loosening their clothing about the abdomen. They complain of flatulence, unsatisfactory, small stools which are often of a dry character, sometimes they are clay colored and have an offensive odor. Nausea is common, vomiting is less common, but does occur. Headaches are apt to be present, likewise coated tongue, loss of appetite, fatigue, restlessness, inability to concentrate, as well as other toxic symptoms.



The colon in a patient with clinical brucellosis who manifested the irritable colon syndrome. The film taken at twenty four hours shows marked irritability and spasticity of the colon, also some ileal stasis.

X-ray studies of the gall bladder were made in this entire series. We employed "Priodax" (Schering) which we found to be highly satisfactory. It was well tolerated and produced little if any side reactions. The x-ray findings were those one would expect to observe in gall bladder dyspepsia. Generally the gall bladder was well visualized. It was of good configuration; the dye was well concentrated. There were no abnormal shadows suggestive of concretions. The emptying time was normal in most of the patients although in some of them it was definitely delayed, while in several the dye was still present as long as 36 hours after ingestion. However in a series as small as this we were unable to draw any fixed conclusions other than that the findings were consistent with the clinical impression of biliary dyspepsia.

The gall bladder and liver have been shown to be the site of infection in brucellosis. The personal experience of Alice Evans is significant. Alice Evans is the worker who made significant contributions to the bacteriology of this disease by demonstrating that the *Br. abortus* and the *Br. melitensis* are two strains of the same organism. She, herself, became infected with the disease. When her gall bladder was removed at operation, it was found to contain an inflammatory focus of brucellosis.

Amoss and others have isolated the Brucella from the bile aspirated by the duodenal tube or obtained at operation. There have been several reports of finding chronic cholecystitis, fatty infiltration of the liver as well as other inflammatory changes and centrolobular necrosis of the liver.

Very significant are the observations of Hoffbauer and Walker who made biopsies of the liver in patients with brucellosis proved bacteriologically. They demonstrated that every patient who had active brucellosis also had hepatic lesions in the sectioned material. In one type of lesion there was demonstrated a periportal infiltration with lymphocytes and plasma cells and occasional necrotic hepatic cells surrounded by mononuclear cells; in the second type of lesion there are areas in which the hepatic cells are replaced by epithelioid cells with an occasional giant cell. The involvement of the liver has been observed with such regularity that many observers now regard the hepatic changes as part of the natural history of the disease; further some writers have advanced the idea that brucellosis is possibly a contributing factor to the genesis of cirrhosis of the liver.

These several reports indicate that brucellosis has both an inflammatory as well as a toxic reaction on the biliary system which is the basis of the biliary dyspepsia syndrome.

THE MIXED GASTROINTESTINAL SYNDROME

Some of the patients presented a mixed syndrome involving several viscera. Thus a patient might experience a feeling of rawness in the epigastrium suggestive of a gastric irritation syndrome while at the same time complaining of intolerance for fried foods, onions, cabbage, etc., with clay colored stools and other symptoms suggestive of a gall bladder syndrome; or he may present any other combination of functional dyspepsias of the digestive tract.

HISTORICAL BACKGROUND

In 1861 Marston described a fever which was endemic in Malta. He designated it as "Mediterranean or gastric intermittent fever." By his description, he identified the disease now known as brucellosis. The disease however was known for many centuries, and clinical descriptions are ascribed to Hippocrates. This dates the disease back to antiquity and beyond.

At present the disease is known to exist widely throughout the temperate zones. On this continent, it is generally believed to have been introduced by Cortez and his conquistadors, probably through the medium of the goats that they brought along as a source of food supply from old Spain. The first actual authentic case in this country was reported by Craig in 1905. However the time of the actual occurrence in human beings on this continent remains a matter of conjecture although it could very well have existed when the first conquistador of Cortez set foot in Mexico in 1519.

From Mexico the disease spread rapidly northward to the United States. By 1911 it was already known and recognized in southwestern Texas where its endemic nature was described by Ferenbaugh who reported upon its prevalence which he believed came from the milk of infected goats.

In 1925, there were 24 cases reported in the United States, while in 1941 there were 3,427 cases reported. In 1938, Angle and his associates examined 7,122 school children in Kansas City by the skin test method and found that the incidence of positive reactors was 9 percent, indicating that this number of school children had had contact with the infection.

In 1945, Benning postulated that there are about 60,000,000 persons in this country living in rural areas or small towns, many if not most of whom are exposed to the dangers lurking in unpasteurized milk, hence to the danger of infection by the abortus type of brucella, and that if 9 percent or even only one percent of this total number have been infected or have had contact with the disease, then the total number of endemic cases in this country becomes quite an impressive and imposing figure. In short, it becomes a public health problem of first magnitude.

In 1887, Bruce described the first of the three groups of organisms which now bear his name. He isolated it from the spleen of a patient who had died of "Mediterranean or gastric fever." The patient had contracted the disease by drinking milk from infected goats. This organism was later designated as Brucella melitensis.

In 1897, Bang isolated the *Brucella abortus* from the foetuses of cows who suffered from a form of infectious abortion of cattle. In 1911, Schroeder and Cotton demonstrated that the organisms were present in the milk of infected cows. In 1914, Traum isolated the third member of this group of organisms, the *Brucella suis* from pigs. Thus there has been demonstrated that there are three strains of the Brucella organisms which are capable of producing clinical brucellosis, namely the *Br. abortus* from cows, the *Br. melitensis* from goats, and the *Br. suis* from pigs.

Culturally the three strains of Brucella have been shown to have different characteristics. *Br. melitensis* is an aerobe. *Br. abortus* grows best under increased carbondioxide tension of ten percent by volume. *Br. suis* is an aerobe. The organisms are very hardy in nature and are highly resistant to destruction by the natural elements. The organisms have been found viable in soil after sixty days and in sterilized tap water after forty-two days. However they are destroyed by exposure to temperatures above 55 degrees Centigrade and by exposure to sun light.

Subsequent investigators have shown that the disease occurs spontaneously in man, sheep, goats, cows, hogs, horses, fowl, dogs, deer and buffalo.

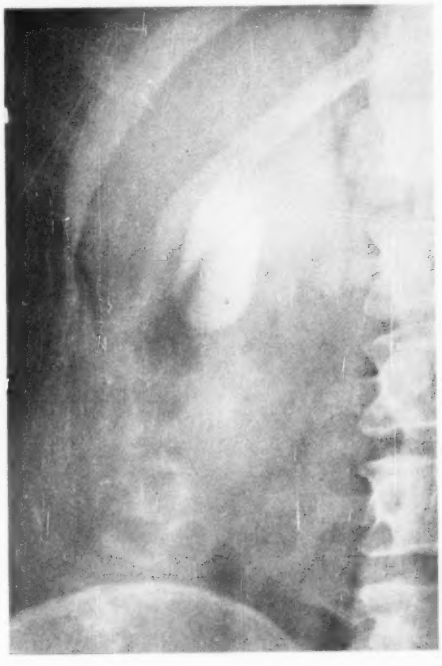
The organisms have been isolated from the following body fluids and tissues: milk, blood, bile, urine, feces, spleen, tonsils, lymph nodes, bone marrow, dental roots, gall bladder, uterus, fetus, vertebra.

An interesting and very important phenomenon of this infection is that animals infected with brucellosis become sensitized to the specific proteins of the brucella organisms in much the same manner that persons infected with tuberculosis become sensitized to the products of the tubercle bacillus.

When an extract of the brucella organism is injected into the skin of a sensitized animal by reason of previous infection, the animal develops a specific skin reaction. Huddleson refers to this extract of the brucella organisms as endoantigen, while others refer to it as an endotoxin. When this endoantigen or endotoxin is injected into experimental animals there results a hyperglycemia followed by a hypoglycemia, also an elevated basal metabolic rate, also a leucopenia in about six hours due to a depression of the neutrophiles in the peripheral blood. When injected into the skin of man or animals it elicits a specific skin reaction which has become the basis of an important diagnostic test. However the organism has a low antigenic or antibody response factor. This low antibody response is the probable reason for the ability of the organism to survive in its host for such a long period of time and produce a long drawn out chronic disease.

When injected into the skin of a previously sensitized animal the endotoxin produces a specific localized reaction consisting of a local capillary dilatation, edema and redness of varying degrees of intensity which may involve an area of one to ten cm. and lasting from one to ten days when it recedes leaving a copper colored discoloration for a similar period. In actual practice the test is read at forty-eight hours. If there is present an area of erythema of over 5mm., the test is considered to be positive. The test as commonly employed today is the Huddleson refinement in which "Brucellergen" is employed; this is the insoluble protein nucleate fraction derived from the cells of mixed cultures of *Br. abortus, Br. melitensis, and Br. suis.*

When this "Brucellergen", the insoluble protein fraction of the brucella organisms is injected into the skin, it combines with the other bacterial proteins which are already present in the body as a result of previous infection. Thus a homologous protein reaction takes place at the site of inoculation which is of the nature of an allergy or hypersensitiveness akin to the tuberculin reaction of tuberculosis. The reaction is strictly a homologous one and depends on sensitization by similar proteins previously liberated by bacterial activity. The nucleoproteins of the brucella organisms do not combine with the proteins of other common pathogenic bacteria, hence the intradermal test is highly specific. Benning explains this



The gall bladder in a patient with clinical brucellosis taken at 36 hours after the ingestion of the dye showing retention of the dye at this time. The patient manifested the syndrome of biliary dyspepsia.

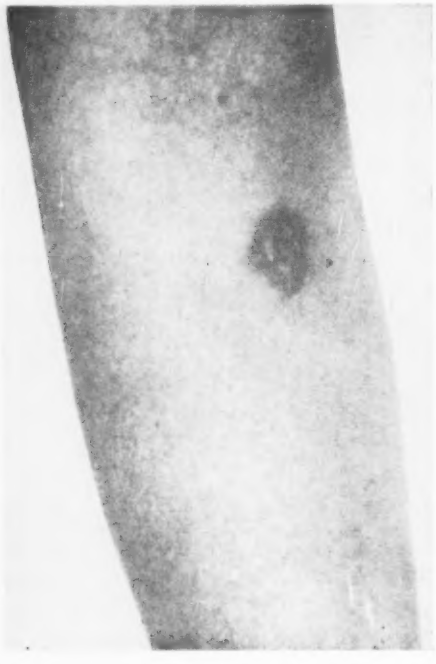
intradermal test by stating that the patient's skin becomes a test tube in which there takes place a conjunction of the nucleoprotein and the antiendotoxin. A positive reaction indicates the presence of bacterial derivatives of the brucella within the tissues of the body. Its specificity is regarded as 100 percent.

In some patients the brucella manifest an antigenic factor and stimulate antibody formation in the form of agglutinins. These will occur in different titers in different patients. Generally a titer of 1:40 is required to designate diagnostic antibody formation; although in some patients the titer may run as high as 1:5,000. However in other patients there is no demonstrable agglutinin formation although the organisms may have been isolated from the patient's blood. Further in some patients the agglutinins if present disappear from the blood rapidly as the disease goes into the chronic state. Evans states that as high as 46 percent of patients with chronic brucellosis have no demonstrable agglutinins and give negative agglutinin tests; while Huddleson gives the figure of negative agglutinin tests in chronic brucellosis as 86 percent. Hence the routine testing of chronic brucellosis by the agglutinin test is of little value as a diagnostic test.

DIAGNOSIS

The diagnosis of chronic brucellosis is difficult to make at times if not baffling and tantalizing. There is no pathognomonic sign for chronic brucellosis, while the clinical manifestations can be so varied and bizarre as to suggest the presence of various other clinical entities.

Alice Evans, Senior Bacteriologist, National Institute of Health, United States Public Health Service, who contracted the disease herself, laments the fact that brucellosis is a very deceptive disease, and that the text book description of neurasthenia resembles that of chronic brucellosis; namely exhaustion, insomnia, irritability, aches and pains for which there is no objective sign; hence many patients suffering from chronic brucellosis are labeled with the dishonorable diagnosis of neurasthenia.



A positive intradermal skin test for brucellosis read at 48 hours showing an edematous area of erythema 4 cm. in diameter.

Harris points out that the textbook description of early tuberculosis resembles the symptomatology of chronic brucellosis, namely fatigue, loss of weight, sweats, cough, slight elevation of temperature, mild chest pains, etc.; all apply equally well to chronic brucellosis as well as to early tuberculosis.

Other writers have pointed out that the disease may simulate neurasthenia, psychoneurosis, bronchial asthma, early tuberculosis, influenza, anemia, syphilis, peptic ulcer, cholecystitis, appendicitis, ulcerative colitis, arthritis, rheumatism, typhoid, endocarditis, coronary disease, functional heart disease, backache, various skin disorders, as well as numerous other clinical entities. Indeed we may call brucellosis the Great Imitator.

There are four laboratory tests which are employed in establishing a diagnosis:

(1) The positive blood culture. This is the one infallible proof of brucellosis infection. Positive cultures may also be obtained from the excrements and bile. However negative cultures are frequently reported in seemingly acute cases of the disease, while the cultures are usually negative in chronic cases. Hence in the study of the chronic case, this test is of little help.

(2) The agglutinin test in a titer of 1:40 or over is considered to be presumptive evidence of the presence of brucellosis infection. Unfortunately this test like the blood culture is too often negative. Negative agglutination tests have even been reported in patients in whom the organisms have been demonstrated in the blood. Manchester of Alliance, Ohio, writing on his experiences with chronic brucellosis states that "agglutination tests sent to the state laboratory were consistently negative." So this test is likewise of little help in the routine diagnosis of chronic brucellosis.

(3) The opsonic index has been employed by some workers. Others regard it as a cumbersome unreliable test of little value in routine diagnosis.

(4) The intradermal skin test is the one test that has met with general approval. It is made by injecting 0.1 cc. Brucellergen which is an insoluble protein nucleate fraction of a mixed culture of the Brucella organisms prepared by the Huddleson method. This test is considered to be practically 100 percent specific when it is positive. There are no false positives. The test is read at 48 hours. If the patient shows an edematous area of erythema of at least 5 by 5 mm., it is considered to be a positive test and indicates contact with the disease. Sometimes the reaction may be as much as 5 to 10 cm. in width. The positive test indicates the presence of brucellosis infection which may be either active or quiescent. Huddleson states that "a diagnosis of the chronic form in many instances is being made on the basis of the skin test alone."

TREATMENT

In spite of the enthusiasm of some recent writers on the subject, it is our opinion that there is no specific cure for the disease and that for the present, treatment is symptomatic and palliative.

Treatment obviously begins with prophylaxis. Upon sober contemplation this phase alone becomes a public health problem of first magnitude. When we consider the large number of cattle that are infected and which form the reservoir for the disease in man, the problem becomes appalling. In the month of April, 1944, over 13,000 cattle were slaughtered in the United States because they had shown positive reaction by the blood test, and in the same month 40,000 calves were vaccinated, according to reports of the United States Department of Agriculture.

As early as 1934, Alice Evans issued the warning that "brucellosis infection is known to occur in animals that appear healthy." This adds to the potential danger of infection from these seemingly healthy animals.

Pasteurization of every drop of milk used in the country would prevent the occurrence of new cases of the Br. abortus type with the exception of such cases incidental to occupational hazards. Colorado has had a state pasteurization law on the books only since June 1, 1949. But total pasteurization is still an ideal to be realized sometime in the future. There are altogether too many loopholes by which it is being evaded, commonly due to a lack of understanding on the part of our rural cousins. There are just too many of them who are not convinced of the necessity of pasteurizing milk for their own use and incidentally for the use of their city cousins and guests. It is pretty difficult to enforce a pasteurization law on a ranch since no milk is being sold there.

However even with pasteurization enforced to the limit, there still remains the great residue of persons who have been infected in previous years. The number of these sufferers probably runs into the tens of thousands in this country, if not more.

Then there is the problem of reinfection. It takes only one glass of unpasteurized, infected milk to infect or reinfect a person. It becomes apparent that the problem of brucellosis is a health problem of major importance.

The organism of brucellosis is known to have a low antigenic or antibody response which explains why the disease becomes chronic due to the prolonged survival in its host. Nevertheless it is our impression that if reinfection can be prevented the disease tends to heal spontaneously in many persons and they become symptom free.

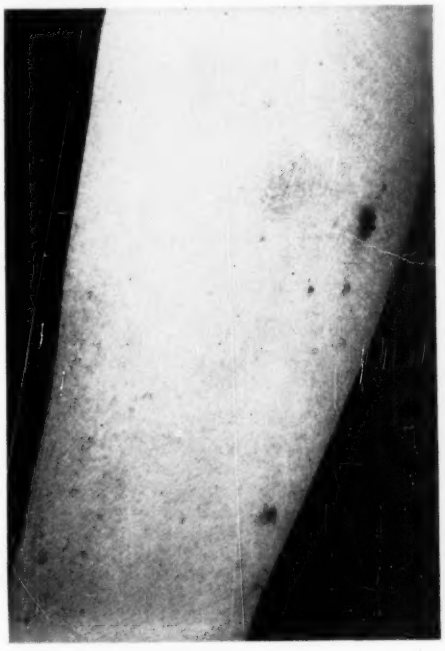
The active forms of treatment which have been recommended for brucellosis are legion. Their very number indicates the lack of specificity on their part. Many of them are symptomatic and palliative.

Since brucellosis has been repeatedly compared to tuberculosis, perhaps a lesson could be learned from the experiences with tuberculosis. The basic treatment of phthisis is rest, good food, fresh air and sunshine. This is an excellent program for chronic brucellosis. Unfortunately the use of sanitarium care is a matter of public education, and the public just has not been educated to enter a sanitarium for the treatment of chronic brucellosis, although it would be an excellent starting point for treatment.

Symptomatic treatment is widely employed in the treatment of chronic brucellosis. It is aimed at the control of the presenting symptoms. Weakness and fatigue are the outstanding symptoms. For these, rest is recommended. For some patients, a short stay in a hospital is desirable. For others this is inconvenient, so advantage must be taken of such opportunities as present themselves for lesser periods of rest, such as retiring early in the evening, relaxing over the week-end. A business man can have his lunch brought in to him at noon and then use part of his lunch hour to relax in, instead of rushing out in traffic to bolt down his meal. One college professor worked out a plan of taking along his sandwich for his lunch and then lying down on his desk to rest for part of the lunch hour. This prepared him for the fatiguing afternoon session with freshman economics students. A newspaper woman learned to take taxi cabs between assignments to save her energy. This helped her to struggle through the fatiguing afternoon. There are infinite other applications of the rest principle, all calculated to reduce the burden of the day's work. Tonics and vitamin preparations may be employed at times.

Restlessness, insomnia and irritability are common symptoms. For these distressing symptoms small divided doses of phenobarbitol are helpful. Other sedatives are also employed.

For the gastrointestinal and biliary symptoms, various principles are employed according to the indications. For the gastric irritation syndrome and the irritable syndrome, the bland diet is useful; while the gall bladder diet is useful for the biliary syndrome. Antacids as aluminum hydroxide gel, trisilicate of magnesium or



A positive intradermal skin test in a patient with clinical brucellosis read three weeks after injection. The edematous area of erythema has been relaced by a copper colored area of desquamation. The two dark spots are refreshed ink identification marks to locate the injection sites of the Brucellergen (upper) and the saline control (lower).

mixtures of these are useful in the gastric irritation syndrome. For the biliary dyspepsia syndrome bile salts are useful. External heat and diathermy may be employed to advantage.

Heart symptoms are common, as tachycardia, palpitation and arhythmia. These call for symptomatic treatment by phenobarbitol, digitalis or quinidine according to the indications.

In secondary anemia, iron, liver, and folic acid preparations are useful.

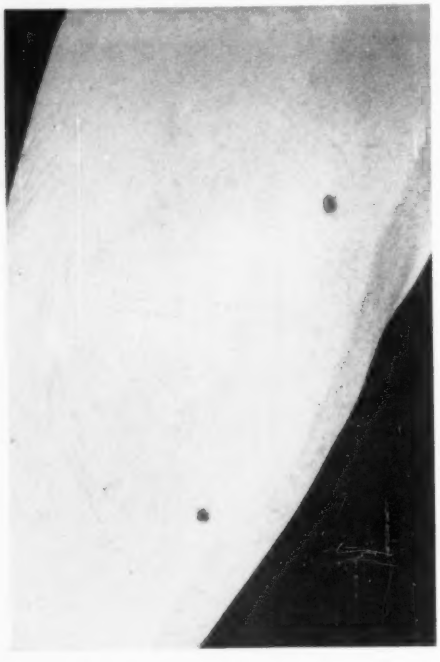
Joint and rheumatic pains are treated by salicylates, diathermy, external heat, baths, and etc.

Vaccine therapy, sera and convalescent sera of all manner have been used equally with all manner of results.

One of these merits attention because of the good results reported by numerous observers, namely Brucellin, a preparation developed by Huddleson. This is a soluble culture filtrate. It is marketed by Sharpe and Dohme. It contains no bacteria but probably a soluble nucleoprotein.

Huddleson states that Brucellin affects the course of the disease by producing a systemic reaction which is accompanied by a neutrophilic leucocytosis. The efficacy of the agent depends on the existence and continuation of a state of sensitization in the patient while under treatment.

Unfortunately there is no standard dose for all patients. Treatment is commonly started by injecting 0.1 cc. Brucellin intradermally to determine sensitization. Thereafter the injections are given intramuscularly, increasing the dose by 0.1 cc. twice a week until the patient gets a systemic reaction consisting of a slight rise in temperature the following day accompanied by muscular pains, chills and sweating. This becomes the therapeutic dose. It is then desirable to give three reacting doses at three day intervals. This is repeated in ten to fifteen days thereafter for six months. In 1933, Huddleson stated that over 2,000 cases of brucellosis had been treated by this method in the United States, Mexico and Malta. Quite likely there were many other thousands treated of which he had no record.



A negative intradermal skin test in a suspect read at 48 hours. The two dark marks are ink identification marks to locate the injection sites of the Brucellergen (upper) and the saline control (lower).

In our experience Brucellin has proved a very valuable therapeutic agent in the treatment of chronic brucellosis. While our series is quite small, we have been favorably impressed with the clinical response manifested by many of the patients to whom it was given. Many of these patients treated with brucellin are not reported here.

Then came the sulfonamides and the antibiotics. It was shown that the sulfonamides alone were of little value. In February, 1948, Spink reported on the use of streptomycin in combination with sulfadiazine. He stated categorically in August, 1948 that "the most satisfactory treatment to date for both acute and chronic cases of brucellosis is a combination of streptomycin and sulfadiazine. He recommended that one half a gram of streptomycin be given intramuscularly every six hours for two weeks, while at the same time three to four grams of sulfadiazine should be given orally as an initial dose, and thereafter 1 gram every four hours for the same two weeks' period. In December, 1948, he stated that there were some strains, the Br. melitensis, which did not respond as satisfactorily as the Br. abortus strain, further that streptomycin was causing vestibular dysfunction in a significant group of cases. Aureomycin on the other hand had the advantage of being administered by mouth and had fewer side reactions. He stated that "a consistent and abrupt change in the clinical course of the disease for the better had been observed in patients receiving aureomycin." He recommended an initial dose of 0.1 gram for the first day to be given in four divided doses, then increasing the dose up to the fourth day when two grams were given in divided doses. This dose is then maintained for ten days. In the addendum to his article he recommended that the daily dose be increased to four to six grams for two weeks rather than the two grams daily dose.

Aureomycin however is not without its side reactions. Nausea is encountered in some patients, occasionally a patient will not tolerate it because of vomiting, in some patients epigastric distress is encountered, also rectal burning and mild diarrhea.

In one batch of aureomycin that we employed, we encountered severe ulcerative pharyngitis and glossitis in three patients to such an extent that we considered it necessary to discontinue the drug. We have not encountered this reaction in any subsequent batch of aureomycin. However we have encountered clinical relapses in several patients treated by aureomycin. We have encountered no serious side reactions since we have employed the crystalline aureomycin.

In December 1949, Spink reported on 22 cases of brucellosis treated with aureomycin. He stated that "to date there have been two clinical relapses and one bacteriologic relapse," and that "patients treated for brucellosis should be followed for at least a year to evalu-

ate the therapy." He also reports two patients treated with chloramphenicol (chloromycetin) with favorable results. Ralston and Payne as well as others report both favorable results and relapses with chloroamphenicol.

Aureomycin, dihydrostreptomycin and chloramphenicol are undoubtedly a very potent group of antibiotics with tremendous possibilities for the control of chronic brucellosis. However it is evident that further studies are necessary to determine the exact dosage to be employed; further a longer follow-up period is necessary to evaluate their precise effects on the disease.

Because we have seen clinical relapses from both aureomycin and dihydrostreptomycin in association with sulfadiazine in our limited series, we have decided that the time is not ripe to discard the older forms of treatment. Accordingly we have adopted the plan of treating new cases of brucellosis with a course of aureomycin or dihydrostreptomycin in conjunction with sulfadiazine for a period of two weeks. For those cases that show clinical relapses, brucellin therapy is then employed; also symptomatic therapy is employed in accordance with the indications of the disease.

PROGNOSIS

Brucellosis is a disease that exacts a low mortality but a high morbidity rate. It impoverishes the physical resources of an individual by producing weakness, anemia, digestive disturbances, joint pains, irritability, insomnia, and a host of other distressing symptoms. The victim begins to think and act like a "neuro." Alice Evans laments the fact that many a victim of brucellosis is labeled with the dishonorable diagnosis of neurasthenia.

Brucellosis is a bacterial disease that elicits a very low antigen response in the body, so that by necessity it tends to become a chronic disease in its natural cycle.

Even the newer and powerful antibiotics do not guarantee a cure, and Spink cautions that even when these are employed that "patients treated for brucellosis should be followed for at least a year to evaluate the therapy."

Perhaps we can learn a lesson from the history of tuberculosis with which it has so often been compared, by employing the terms "quiescent" and "arrested" rather than "cure."

The disease often becomes quiescent and arrested after treatment with brucellin and the newer antibiotics, also it often heals spontaneously if reinfection can be prevented.

The prognosis however is always guarded.

CASE REPORT

A single case report is herewith presented in detail to illustrate the gastrointestinal syndrome presented by a patient with chronic brucellosis and the difficulties encountered in arriving at a correct diagnosis. A routine skin test would have established the correct diagnosis in the first place and saved time, had it been made.

Because of this and other similar experiences, we are making a greater number of intradermal tests for brucellosis in the examination of our private cases especially in those complaining of chronic fatigue.

M. A., a lady of 40 years came to the office complaining of trouble with her digestive tract six months in duration. She described a sensation of rawness in the epigastrium which was not related to the food cycle. Some types of foods disagreed with her, but there was no consistent pattern in the food disagreements, although generally she felt better on a bland diet. At times the sensation of rawness spread to involve the entire abdomen. The diffuse abdominal distress was not related to the food cycle and was irregular in its duration. It might last minutes or hours and it might occur at any time of the day or night. She also complained of excess belching, bloating and gas which was worse after a heavy meal although it might occur at any time. She did not pass mucus in the stools at any time. She was constipated, passed small pencil stools of normal color. She had learned to take Metamucil which had given her some relief. Her weight was constant, her appetite was fair. She felt tired much of the time.

Physical examination showed an adult white woman 40 years old weighing 146 pounds, 5 feet 4 inches in height, not acutely ill but anxious and restless in appearance. The pulse was 82, the blood pressure was 156/70. She was of stocky habitus. The eyes reacted to light and accommodation, there was no ptosis and no strabismus. The throat was clear, the teeth and gums were in good condition.

The heart borders were normal and the heart tones were clear, there were no murmurs. The lungs had good resonance, there were no rales and no rubs. The abdomen was of normal configuration. An old appendectomy scar was present. There was slight diffuse tenderness over the entire abdomen and slight diffuse muscle spasm. The liver and spleen were not palpable. The descending colon was spastic, tender and palpable. The uterus was small and movable, the adnexa were not palable. The reflexes were present and equal.

The urine was within normal limits. The W.B.C. was 7,400, the R.B.C. was 4,800,000, the hemoglobin was 80%; the differential was 65 percent polys, 30 percent lymphs, 2 percent eosinophiles, and 3 percent transitionals. The sedimentation rate was 5 at one hour. The Ewald test meal showed a free acidity of 25 and a total acidity of 55 at one hour, the digestion was good, blood was not present.

X-ray examination of the gall bladder by oral dye method showed the gall bladder to fill well. It was of good configuration and concentration. The emptying time however was markedly delayed. At 36 hours the gall bladder was still visualized. Longer observations of the gall bladder were not made. The stomach was normal in size and of intermediate shape. There were no defects. Vigorous peristalsis was noted. The rugae were normal in appearance. The duodenal cap was quite irritable, but under manipulation it was seen to fill well. At six hours, the stomach was empty. At twenty-four hours, the meal was present in the colon from the caecum to the rectum. The colon was markedly irritable and spastic in appearance.

A diagnosis was made of Gastric Neurosis, Spastic Colon and Gall Bladder Dyspepsia. The patient was placed on a bland diet with eggs omitted, given iron bile salts (Bilron) and a prescription containing a third of a grain of phenobarbitol in Elixir of Bewon to be taken after meals. Also she was given gluco-calcium once a week intravenously and kept under observation. She remained on this program for three months and at the end of this time she had made little improvement. The symptoms had not subsided, and she felt no better. In fact they were just as annoying as at the time of the initial examination three months previously.

Because of the possibility of an underlying neurosis, psychiatric inquiry was made at this time, but it brought out nothing of importance. The lady was happily married; she had a pleasant and comfortable home, she enjoyed her family life. Her social and church activities took up her surplus energy and she enjoyed both of them thoroughly. There seemed to be no conflicts, no inhibitions, no frustrations.

Since the ambulatory, symptomatic treatment had accomplished little in her case, it was suggested to her that she should enter a hospital for rest and observation, which she did. After a few days in the hospital, attention was immediately directed to the afternoon temperature which rose to 99.2 to 99.6. The morning temperature had remained normal. This directed attention to the several causes of afternoon elevation of temperature. Considering the several possibilities, it was noted that there was no diarrhea, no cramps, no tympanitis, no rose spots, no enlarged spleen; no cough, no chest pains, no night sweats, no sputum; no joint pains. There was no clinical evidence of typhoid, tuberculosis, or rheumatic fever. However brucellosis came into consideration. At this time the patient recalled that about a year previously she had visited a farm where she had taken unpasteurized milk. It had come fresh from the cows. An intradermal skin test was made with Brucellergen, the insoluble protein nucleate fraction derived from the brucella organisms. This proved to be strongly positive and gave a raised swollen, edematous area of erythema about 4 cm. in diameter. It persisted for two weeks and subsided gradually leaving a copper colored area which desquamated for another two weeks.

However as soon as the clinical diagnosis of brucellosis became apparent, the patient was given a course of aureomycin for a period of two weeks. After four days, the temperature became normal and remained normal, and she left the hospital feeling entirely free of her digestive symptoms.

Comment. This patient undoubtedly had brucellosis at the time of her first examination three months previously which had been contracted about nine months before that time, probably at the time she had taken the unpasteurized milk on the farm. At the time of her initial examination none of the common signs of brucellosis were in evidence. There was no fever, no sweating, no joint pains. (Brucellosis is also called Undulant Fever because sometimes it has undulating waves of normal temperature alternating with fever periods.) Instead she presented a gastrointestinal syndrome consisting of abdominal distress, both epigastric and diffuse, which were not related to the gastric cycle, also belching, bloating and flatulence which occurred principally after a heavy meal. This led to the impression of the existence of a functional digestive disorder due to gall bladder dyspepsia, gastric neurosis, and irritable colon.

The diagnosis of chronic brucellosis was suggested when the patient gave evidence of daily afternoon fever while under observation in a hospital months later. The strongly positive intradermal test of brucellosis was considered sufficient in establishing the diagnosis.

SUMMARY

Chronic brucellosis is a disease of many clinical manifestations, and one of these is functional disorders of the digestive tract.

An analysis of twenty cases shows that these functional disorders of the digestive tract are apt to fall into four classes, (1) a gastric irritation syndrome, (2) an irritable colon syndrome, (3) a biliary dyspepsia syndrome, (4) a mixed dyspepsia syndrome.

Brucellosis is endemic in Colorado, as well as in much of the United States. Colorado has had a state pasteurization law on the books only since June 1, 1949.

Much of Colorado's population is still exposed to the danger of infection because of its habit of eating in all manner of out-of-the-way, as well as in rural eating places where it is difficult to enforce pasteurization.

The organism produces a very low antigenic or antibody response in the body, which explains the ability of the Brucella to survive in its host for long periods of time and to produce the chronic drawn out type of disease which it causes.

The organism elaborates a toxin in the system of its host which sensitizes the skin to reactions by injection of the soluble protein nucleate fraction of the Brucella (Brucellergen). This is the basis of the intradermal test.

The underlying pathology of the digestive syndromes is an inflammatory and a toxic reaction of the involved viscera. It has been suggested that brucellosis is a contributing factor in the genesis of cirrhosis of the liver.

There is no pathognomonic sign for chronic brucellosis, and frequently the disease may simulate other conditions. Brucellosis may be called the Great Imitator. The best and often the principal diagnostic sign is the intradermal skin test performed with Brucellergen.

There is no specific cure for this disease at present. Treatment is symptomatic and palliative. Relapses are frequent.

Prophylactic treatment consists in rigid pasteurization of milk. There remain however the occupational hazard cases, and the great number of patients who are already infected.

Active treatment consists in periods of rest for the fatigue and weakness augmented by the use of vitamins and tonics. Symptomatic treatment is directed for relief of symptoms in the digestive tract, the cardiovascular system, the musculo-skeletal system, the respiratory system, etc., according to the indications.

Aureomycin dihydrostreptomycin together with sulfadiazine and chloramphenicol have been tried and are useful, but further observation is necessary to evaluate their therapeutic effects.

Brucellin, a soluble culture filtrate developed by Huddleson, is a very useful biologic product in treatment. It has given good results.

Brucellosis is a stubborn, chronic disease. The disease often becomes arrested or quiescent under treatment, also it often heals spontaneously if reinfection can be prevented. The prognosis is always guarded.

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PEPTIC ULCER PERFORATION INTO THE LESSER PERITONEAL SAC
I. A STATISTICAL STUDY OF 57 COLLECTED CASES

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IN a recent study of peptic ulcer perforation, my attention was directed to a lack of information pertaining to perforations involving the lesser peritoneal sac. This form of perforation is not mentioned in most textbooks. A perusal of the literature revealed only one article on this subject and a few articles on lesser peritoneal cavity involvement, complicating pancreatic and biliary conditions. The various medical indexes do not reveal the subject under this title. It is possible that the condition has been wrongly indexed, or that lesser peritoneal sac perforations are reported together with those of the greater peritoneal cavity. Most of those who answered the questionnaires mention the fact that their record files do not differentiate between lesser and greater peritoneal sac perforations. On the other hand, the majority of those who returned their questionnaires did not have a single case.

It is the purpose of this communication to present a statistical study of peptic ulcer perforation into the lesser peritoneal sac. Since the condition is uncommon, it was thought the best way to adequately establish factual data on this subject was to send out a questionnaire. Questionnaires were mailed to 350 of the leading surgeons and gastroenterologists throughout the country. Of these, 75 replies were received, 48 of which gave suitable information for statistical study. All of the data obtained from this source is presented in order to make the material available to others seeking information on this subject. This study forms part of a clinical research problem on peptic ulcer perforation into the lesser peritoneal sac. The clinical and roentgenological aspects will be considered more fully in a separate report to be published soon.

The incidence of lesser peritoneal sac perforation has never been established. Many of the leading surgeons and gastroenterologists stated that they have never had a case of lesser peritoneal sac peptic ulcer perforation. Of the 48 satisfactory questionnaires, 26 had had no cases. The incidence given in the questionnaire ranged from 0.1 percent to 6 percent. The majority of those who returned satisfactory questionnaires, were unable to give any information regarding the incidence of this condition. Among 1,583 collected surgically proven cases of peptic ulcer perforations, there were 16 with perforations into the lesser peritoneal sac, an incidence of 1 per cent.

As expected, from the lack of literature on lesser peritoneal sac perforations, the condition was found to be comparatively rare, occurring in only 1 per cent of cases of peptic ulcer perforations. This is the surgical incidence, but one must also consider the fact that there are a number of cases in which slight leaks occur into the lesser sac, of the "formes frustes" type that are not even recognized.

Of the 48 satisfactory replies, 22 gave information on one or more cases. A tabulation of the collected cases totaled 57. There were 56 peptic ulcer perforations and 1 perforation following a gastroscopy. Of these, 30 were gastric, 15 duodenal, and in 12 the exact site was not mentioned. Table 1 presents the cases according to the site of the perforation.

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TABLE 1

Site of gastric ulcer perforation	Cases
Posterior wall	7
Lesser curvature, posterior wall	15
Greater curvature	1
Fundus	4
Pylorus, posterior wall	3
Site of duodenal ulcer perforation	
Posterior wall	15
Site not mentioned	12
Total cases	57

Since the lesser peritoneum is attached to the posterior aspect of the stomach and duodenum, the site of the perforated ulcer must therefore be located posteriorly. It will be seen from the above table that all of the perforations occurred on the posterior wall.

It is noteworthy to point out the difficulty encountered in the clinical diagnosis of lesser peritoneal sac perforations. In the 57 collected cases, the diagnosis was established by surgery in 48, by autopsy in 7 cases, and was not mentioned in 2. Of the 57 cases an exact pre-operative diagnosis of lesser sac perforation was made in only 2 cases. In 20 instances the query of diagnosis was not answered. A perforated ulcer was diagnosed 32 times, acute pancreatitis in 1 case and intestinal obstruction in 1 case. All of the cases were either acute or sub-acute. The lesser peritoneal sac involvement was not suspected in all but 2 cases.

The symptoms mentioned in the cases of lesser peritoneal sac perforation were not diagnostic. Most of the cases presented an acute surgical abdomen, although there were many with mild symptoms. The following symptoms were mentioned in the collected cases: abdominal pain, localized or generalized, mild or severe; shock; abdominal rigidity; and abdominal distention. In one case there was a subcutaneous emphysema. The pain in some instances radiated to the back or to the right shoulder.

According to the information recorded in the questionnaires the roentgen examination was of little value in establishing an accurate diagnosis of lesser peritoneal sac perforation. However, roentgen diagnosis of a perforated viscus was made in over 70 per cent of the cases. In only 2 cases was a correct roentgen diagnosis made; in these, barium had escaped into the lesser sac. Table 2 presents the roentgenologic findings in 40 of the 57 collected cases.

TABLE II

	Cases
No x-ray findings	10
Gastric ulcer niche	2
Air beneath the diaphragm	24
High fixed diaphragm	1
Gastric retention	1
Barium in lesser peritoneal sac	2
Paralytic ileus	1
Enlarged duodenal curve	1

In 17 of the 57 cases no x-ray examination was made. In most of these the failure to perform x-ray studies was due to the acuteness and severity of the condition. It is interesting to point out that of the 40 cases x-rayed, 24 revealed air beneath the diaphragm. The side in which the air was demonstrated was not mentioned in most instances, but those who did make a statement regarding the side the air was located reported it to be on the right side. In only one instance was there any mention of air being observed on the left side. The fact that free air was noted beneath the right diaphragm is diagnostic of a perforated viscus, but this alone does not necessarily indicate the presence of a lesser sac perforation. I believe that the difficulty in the roentgen diagnosis of this condition is due in many instances to the lack of roentgen criteria, which has as yet not been fully established. This phase will be presented in a later research problem to be published soon.

CONCLUSIONS

1. This review presents the data obtained in a series of 57 collected cases of peptic ulcer perforation into the lesser peritoneal sac.

2. The surgical incidence of lesser peritoneal sac perforations among perforated peptic ulcers is 1 per cent.

3. The site of all perforations into the lesser sac occurred on the posterior wall of the stomach and duodenal bulb. Gastric perforations predominated.

4. The exact clinical diagnosis of lesser peritoneal sac involvement of a peptic ulcer perforation was not made in 55 of the 57 cases.

5. Roentgen examinations were made in 40 of the 57 cases. In 24 air was demonstrated beneath the diaphragm. In only one instance was mention made of air being observed under the left diaphragm. In 2 cases, barium was demonstrated in the lesser peritoneal sac.

The author wishes to express his gratitude and thanks to all those who returned the questionnaires for making available their records and experiences.

To Doctors M. M. Zinninger and Wm. T. McElhinney of the Cincinnati General Hospital, I am especially grateful for the large number of cases and detailed information given.

SUCCESSFUL MANAGEMENT OF INFANTILE DIARRHEA IN A GENERAL HOSPITAL

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INTRODUCTION

THE study of electrolyte and fluid disturbances in disease is at times confusing and complex to the clinician. Certain basic physiologic principles are more clearly visualized when one specific disorder is studied. There is no better opportunity for such an investigation than that afforded by a study of infantile diarrhea. Through such an analysis, a set of simple instructions have been formulated which, when adhered to, offer facility, simplicity and satisfactory therapeutic results. This is of prime importance in the general hospital where internes and residents may, during the course of their training, encounter such problems. It is also of value to the clinician who has become overly conscious of the academic importance of balance studies, the role of the potassium ion and detailed laboratory data.

The results and material presented in this discussion concern that type of infantile diarrhea which is characterized by its negative findings in so far as necropsy, bacteriological and epidemiological studies are concerned.

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Of great significance is the fact that this type of diarrhea manifests itself with *rapid* and profound metabolic, electrolytic and fluid derangements, the treatment of which must be quickly and accurately executed. The results and conclusions of this paper are based upon a study of 25 such cases in the Mercy Hospital during the past 2½ years.

The following does not deal with detailed determinations of the various chemical components of the body fluids in these infants. Such determinations, clinically, appear to us to be not only unnecessary, but detrimental. For, through the withdrawal of 15 to 20 cc. of blood by venipuncture, the blood volume is of necessity depleted. This occurs in a disease state which is accompanied by a diminished blood volume. Actually, the withdrawal of such a quantity will lower the blood volume in a 3 Kgm. infant approximately 15 percent. This reduction may lead to impairment of the renal defense mechanisms which aid in maintaining the normal electrolytic pattern of the body fluids and could possibly produce circulatory collapse. There is the need for the withdrawal of only one-quarter (4 cc.) of this amount of blood for a logical guide to therapy and a better understanding of the condition at hand.

PATHOLOGIC PHYSIOLOGY

A brief review of the pathogenesis of this disturbance is essential for an adequate understanding and rationale

for therapy. With the onset of diarrhea there is a loss of fluid through frequent watery bowel movements. This loss has been estimated by Holt, et al. (1) to be as great as 300 cc. in 24 hours. The seriousness of this great loss is still better appreciated when it is realized that the body is also deprived of large quantities of electrolytes, chief of which is the sodium ion, together with fluid, through the loss of gastrointestinal secretions which would normally be reabsorbed by the bowel. In addition, anorexia and vomiting further add to fluid and electrolyte deficit. The deprivation of intake resulting from the latter two phenomena is of equal importance. Gamble (2) has demonstrated that dehydration and electrolyte deficits do not occur in the normal infant as long as the oral intake is maintained at about one-fourth of its normal value. However, in an infant suffering from diarrhea to the extent that 300 cc. of fluid are lost daily in the stool, this intake must be maintained at about two-thirds of its normal value. The reduction of intake produces caloric deficits, the results of which are manifold. First, there is formation of ketone bodies due to carbohydrate deprivation. These products of faulty metabolism by nature of their being organic acids, require sodium for neutralization. This adds strain to the already depleting or depleted store of this cation. The second effect is upon the cell. Cellular protein is utilized for energy, causing a loss of cellular water and a depletion of the cellular cation, potassium. Lastly, there is added the effect of the intoxication resulting from the disease itself. Thus, with such events there occurs a marked reaction change in the blood; a state of acidosis which, if prolonged, or of sufficient intensity, results in death.

Fortunately, there are certain mechanisms which come to the defense of such a dereliction of the body fluids and electrolytic arrangements. The maintenance of hydrogen ion concentration of body fluid between pH 7.35 and 7.45 allows for normal physical and metabolic function. The basis for the control of this narrow range lies in the slight degree of hydrogen ion dissociation in carbonic acid. This dissociation is further limited when bicarbonate ion is added from the sodium bicarbonate of the extra cellular fluid. Thus, the carbonic acid, bicarbonate ratio comprises the chief buffer system of the extra cellular fluid compartment. As protection against the distortion of this main line of defense there is the respiratory control of carbonic acid. Here, as a result of decreasing the concentration of carbon dioxide in the alveoli by mechanical expansion, a normal buffering ratio of carbonic acid to sodium bicarbonate of 1:20 is approached. However, this defense mechanism has certain inherent weaknesses and is prone to be only about 50 percent effective (2). Therefore, with significant sodium losses, this defense becomes wanting.

Another defense of importance is that supplied by the kidney. It is the chief defender of the normal physico-chemical structure of body fluids. This is accomplished through one or more of several of the following mechanisms: (1) the excretion of a more acid urine by the conversion of dibasic-phosphate into the monobasic form; (2) the regulated substitution of ammonia leading toward sodium conservation; and (3) the selective excretion of certain anions leading to the preservation of the bicarbonate ion.

As previously mentioned, this malady is accompanied by diminished blood volume, which markedly influences kidney function by causing diminished glomerular flow. Thus, it may be seen why the renal mechanism so often fails in infantile diarrhea.

The insensible water loss and the obligatory expenditures in the infant must be considered. Since the losses through these channels are relatively large in comparison with the small extra cellular fluid compartment or reservoir which supplants such losses, the infant is placed in a precarious position when he suffers from diarrheal disease.

Other defense mechanisms, primarily concerned with fluid conservation must be mentioned. The initial step in such a defense is the shunting of fluid from the interstitial and intra-cellular compartment into the vascular compartment (3). Although this phenomenon is physiologically advantageous to the preservation of a normal blood volume, it upsets the normal cell protein-water ratio leading to a loss of cellular potassium. Thus, dehydration involves not only the extra cellular compartments of body fluids, but also the cellular compartments.

THERAPY

The following, based upon the preceding discussion, is an outline for a systematic and simplified approach to the treatment of infantile diarrhea:

1. The admitting doctor must take a complete history stressing the duration of illness and amount of oral fluid or formula taken during the illness. Isolation technique is employed.
2. 4 cc. of blood by venipuncture is obtained for a CO_2 combining power determination. Stool for culture and nose and throat swab are taken.
3. Weigh baby.
4. If no nausea and vomiting are present, a formula of skim lactic acid milk and supplementary glucose and water feedings may be used.
5. If CO_2 combining power is below 40 volumes percent, the following repair solutions must be administered by means of a cut-down technique:
   (a) CO_2 combining power 30 to 40 volumes percent administer.
      (1) 1/6 molar sodium lactate solution, amount determined by Hartmann formula; 4 cc = CO_2 combining power X weight in Kgms. x 0.3 and/or
      (2) Lactate Ringer's Solution.
   (b) CO_2 combining power below 30 percent.
      (1) Sterile 5 percent sodium bicarbonate solution, amount determined by use of Hartmann formula, is used.
      cc = 20 (normal CO_2 combining power minus infant's CO_2 combining power x wt. in Kgms. x 0.026).
      (c) If CO_2 combining power is above 40 volumes percent, subcutaneous 5 percent glucose in saline may be used to supplement oral feedings.
6. Glucose in saline and glucose in water to be given so that the total intake of fluid is slightly more than 3 ounces per pound of body weight per 24 hours.

7. Careful daily observations as to the following must be made:
   (a) Number and character of stools.
   (b) Total intake via cut-down or oral feeding.
   (c) Urinary output.
   (d) Signs of overhydration.

Discussion of therapy: The chief aim of active therapy is toward the correction of the reaction change of the blood. If the condition is of moderate degree, 1/6 molar sodium lactate solution may be employed. However, if of severe intensity, a sterile 5 percent sodium bicarbonate solution is necessary, since it quickly replaces sodium as well as the essential bicarbonate ion. The preference of the bicarbonate solution to sodium lactate lies in the fact that the latter requires normal oxidative processes for the removal of the lactate radicle. It may be presumed that these normal metabolic activities are impaired during this malady. Since it takes relatively little carbonic acid to establish a normal carbonic acid-sodium bicarbonate ratio, the danger of inducing alkalosis by such treatment is perhaps unduly exaggerated. Further, one may feel safe in regards to over-alkalinization by using the Hartmann formula to compute the amount of solution necessary. To utilize this formula the CO_2 combining power of the blood must be known. The test requires 4 cc. of oxalated blood, and it is perhaps the only indication for the removal of blood by venipuncture during the acute phase of this condition.

The success with sodium bicarbonate solution has been dramatically shown by this study. Infants who, upon admission, were extremely moribund, with CO_2 combining power levels at 15 volumes percent or less, showed definite clinical improvement within several hours after the use of bicarbonate therapy. Concomitantly, saline solution is used. This will aid in the restoration of normal blood volume. Saline, however, is not water and it will be retained in the body to a large extent. One must recognize the phenomena of overhydration. Quantitatively, about 200 cc. of saline, or that amount of fluid lost by stools, plus that necessary for a daily obligatory expenditure is necessary in a moderate case. The remainder of fluid necessary to supply that loss through insensible sources should be supplied as glucose in water. Mild overhydration has taken place on occasion in our series. Fortunately, it was quickly recognized and serious harm was not done. Incorporation of glucose in all repair solutions is advantageous through its antiketogenic and protein sparing effects.

No mention has been made concerning the replacement of potassium ion. We have had no experience with potassium repair solutions. Certain factors must be mentioned in regards to their use. The solutions contain potassium at varying concentrations greater than the normal serum concentration of the ion (5). Therefore, to use a potassium solution before there is absolute certainty of good renal function, may, due to accumulation of potassium ion, result in cardiac embarrassment. Also, with deranged cellular metabolism present as a sequela of the diseased state, there is no proof that the cell would be able to utilize the potassium offered. Lastly, if the reaction change and blood volume are immediately attended to, the infant is capable of resuming oral intake within 24 to 36 hours, and the need for potassium or other active parenteral therapy ceases (6).

No antibiotic or chemotherapy appears to influence the progress of the malady (7). It is a wise procedure, however, to administer penicillin as a prophylaxis against respiratory complications, especially in those infants exhibiting acidotic coma. The use of gastrointestinal demulcents do not appear to alter the course of this disease.

RESULTS

Abiding by the principles of therapy mentioned, this series showed only two deaths in 25 infants. Necropsy examination revealed one death due to massive lobar pneumonia. This prompted further use of prophylactic penicillin. The other fatality was due to bilateral subdural hematomata. The remainder of the cases made uneventful recoveries.

The following cases illustrate the application of therapy and are typical of the series.

Case 1. Infant G. Born January 3, 1949 in a foundling home; uncomplicated delivery; birth weight 5 lb. 13 oz.; on formula feeding from time of birth. On January 14, 1949, 7 liquid stools occurred. For the next 5 days it had 8-9 stools per day with weight loss of 1 lb. 8 oz. Infant admitted to Mercy Hospital January 19, 1949, with obvious dehydration as evidenced by poor tissue turgor, depressed fontanelles, and moderate air hunger. Although not vomiting, oral intake was limited to a few sips of sterile water in the preceding 24 hours. CO_2 combining power on admission was 28 volumes%. 30 cc. of sodium bicarbonate solution and 500 cc. of 5% glucose in saline were given in the first 24 hours. Within 8 hours air hunger ceased. On January 20, 1949, was given 250 cc. of 5% glucose in Ringer's lactate sol. and 250 cc. of 5% glucose in sterile water. By January 21, 1949, hydration was good and baby readily accepted skim lactic acid milk feedings by mouth. Other therapy constituted penicillin 50,000 U q 6 hr. Stool culture and nose and throat culture neg. Baby was discharged clinically well January 29, 1949.

This case illustrates prompt recovery in a moderately severe instance of acidosis (CO_2 28vol.%), following administration of sodium bicarbonate solution, 5 percent glucose in saline, and Ringer's lactate.

Case 2. Infant S. Born December 30, 1948 in a foundling home; uncomplicated delivery; birth weight 6 lb. 3 oz.; on formula feeding since birth. Stools were normal until January 19, 1949, when became yellow and "loose." Admitted to Mercy Hospital January 19, 1949 with signs of mild dehydration. CO_2 combining power was 40 volumes percent. Therapy consisted of penicillin 50,000 U q 6 hr., subcutaneous injection of 50 cc. of 5% glucose in saline q 4 hr. for 36 hours. At end of 24 hours hydration was good and parenteral therapy was supplemented by skim lactic acid milk by mouth. Stool and nose and throat cultures were neg. Infant was discharged January 28, 1949 clinically cured.

This case illustrates recovery from mild dehydration by use of subcutaneous injection of 5 percent glucose in saline and oral feedings.

Case 3. Infant M. J. B. Born August 5, 1948 in a foundling home; uncomplicated delivery; weight 5 lb. 6 oz.; on formula since birth. On August 13, 1948 onset of diarrhea. Oral intake was well maintained. Admission to Mercy Hospital August 14, 1948 with evidence of mild dehydration. CO_2 combining power on admission 50 volumes percent. Skim milk formula was substituted for whole milk formula and despite continuance of diarrhea infant accepted her feedings. Diarrhea ceased on August 16, 1948 and hydration was normal. Discharged August 22, 1948 clinically well.

The above illustrates a case of mild dehydration and mild acidosis which did not require parenteral therapy because of maintenance of oral intake.

SUMMARY AND CONCLUSIONS

A brief review of the pathologic physiology of infantile diarrhea has been presented so as to formulate a simple rational form of therapy. The results from such

therapy in a series of 25 infants has been excellent. Thus the following conclusions are tenable:

1. The use of sodium bicarbonate in severe cases of acidosis is safe and satisfactory.

2. The withdrawal of large samples of blood from infants for extensive laboratory tests is unnecessary and may be harmful.

3. The CO_2 combining power affords a guide to therapy.

4. The maintenance of fluid intake, oral and/or parenteral is of prime importance in this disorder.

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THE CHOLAGOGIC AND CHOLERETIC EFFECT OF SODIUM NICOTINATE

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INTRODUCTION

MARKED elevation of the indirect reacting bilirubin of serum follows the intravenous injection of 30 mgs. of sodium nicotinate in normal subjects (7,6,10). It reaches a maximum value 60-90 minutes after the injection and slowly returns to the original level in 6 to 8 hours. The mechanism of the hyperbilirubinemic effect of sodium nicotinate and its application to the study of the metabolism of biliary pigments and to the diagnosis of liver disorders have been described in a previous communication (10). In the course of that study, evidence was obtained that the drug possessed marked cholagogic effect. This observation is confirmed and extended by further findings presented in this paper.

EXPERIMENTS AND RESULTS

Eighteen healthy adults, who had been fasting for the past twelve hours, volunteered for the following experiment. A Rehfuss tube was passed into the duodenum under fluoroscopic control and its extremity connected with a volumetric drainage bottle. The results were similar in all volunteers. Few cc. of yellow colored bile were obtained in some subjects, but the scanty flow soon stopped altogether. Half an hour later, when the subject had become well used to the presence of the tube, thirty mgs. of sodium nicotinate in 10 cc. of saline solution were injected intravenously at the speed on about 30 seconds per cc. The injection was followed by a generalized flushing, particularly evident over the face and extremities, and, at the same time, the subject experienced a marked feeling of warmth. These effects of the drug usually regressed in two to five minutes time.

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Ten minutes after completing the injection of sodium nicotinate, a copious rhythmical flow of bile began, in the quantity of 2 to 4 cc. per minute. About 10 to 15 cc. of light colored fluid (bile A) were collected in the first 2 to 6 minutes. From 175 to 200 cc of dark brown colored bile (bile B) followed in the next 20-25 minutes. Finally, 40-50 more cc. of golden yellow colored bile (bile C) were obtained slowly during another half an hour, at the end of which the flow stopped altogether. The collected samples revealed a concentration of bilirubin and biliary salts in the range of normal values. The total volume of bile collected was of 220-270 cc., a figure much higher than the 50-110 cc. usually obtainable with the stimulation by means of hypertonic magnesium sulphate solutions.

It appeared then that the solution nicotinate technic produced a more pronounced cholagogic effect than the Meltzer-Lyon's procedure. To further demonstrate this a Rehfuss tube was again passed in the duodenum of three more healthy subjects. Bile flow was first stimulated by means of duodenal instillation of 100 cc. of a 25% solution of $MgSO_4$. When bile could no longer be obtained, sodium nicotinate was injected intravenously. Following this, between 105 and 175 cc. more of mixed bile were collected, in one hour time. The intravenous injection of 100 mgs. of nicotinamide, which is not followed by elevation of the serum bilirubin level (10), also had a similar but much less pronounced cholagogic effect. Nicotinic acid and nicotinamide were also moderately active when given orally.

As the samples of bile collected during the experimental period were of much larger volume but did not present higher concentration of bilirubin or biliary salts, the effect of sodium nicotinate in normal subjects appeared to be mainly cholagogic. A clinical case who came to our observation, however, offered the opportunity of showing that sodium nicotinate and nicotinamide may also possess choleretic action when retention of biliary pigments is present. The patient, deeply jaundiced with evidence of serious liver damage, had a

TABLE I: The effect of the intravenous injection of sodium nicotinate on the serum bilirubin and bile bilirubin and biliary salts level in a patient suffering from chronic hepatocholangitis with surgical biliary fistula.

Time after injection (hours)	0	1	2	3	4	5	6	7	8	24	48
Serum, total bilirubin mgs%	5.09	7.49	8.09	8.31	8.64	8.29	7.94	7.60	7.34	7.50	7.02
Serum, direct reacting bilirubin mgs%	1.18	1.54	1.87	2.18	2.36	2.29	2.24	2.11	2.00	1.54	1.27
Serum, total bilirubin mgs%	0.52*	1.94	4.82	11.73	18.61	16.43	15.27	13.28	10.47	7.32	5.28
Bile, biliary salts 0/00	2	4	8	16	32	16	16	16	8	4	2

*The strikingly low initial value of bile bilirubin concentration was likely due to the impaired liver function of the patient.

TABLE II: The effect of prolonged treatment with nicotinamide (300 mgs. a day, intramuscularly) on the serum level of bilirubin and biliary salts, bilirubin concentration in bile and urine, and fecal and urinary urobilinogen in a patient with severe hepatic dysfunction presenting a surgical biliary fistula.

Day of treatment	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Serum																
Total bilirubin (mgs.%)	5.14	4.88	4.64	4.59	3.57	2.49	2.45	1.98	2.51	2.42	3.73	3.89	4.10	4.45	4.90	4.85
Direct reacting bilirubin (mgs.%)	1.91	1.67	1.63	1.75	1.81	1.75	1.22	0.93	1.21	1.37	1.54	1.62	1.73	1.89	1.76	1.79
Bile salts 0/00	4	4	4	4	4	0	0	2	0	4	8	4	4	4	4	4
Bile																
Total bilirubin (mgs.%)	2.4	2.8	3.5	4.2	5.0	5.6	10.2	13.5	7.8	11.5	6.2	4.1	3.8	2.7	3.0	3.4
Bile salts 0/00	32	64	32	128	128	64	256	256	64	32	32	16	8	8	16	8
Urine																
Bilirubin (mgs.%)	2.5	1.8	0.7	0.4	0.4	0.3	0.1	0.8	0.9	0.2	0.6	1.7	1.8	2.6	2.4	2.1
Urobilinogen (mgs.%)	12.6	11.7	12.0	13.0	13.2	14.9	16.0	17.5	21.3	19.2		14.1	12.5	10.7	9.4	10.3
Feces																
Urobilinogen (mgs.%)	10.2	12.0	14.1	19.7	24.8	32.6	51.4	47.5	52.0	55.4	34.9	32.15	28.9	27.2	19.4	23.5

biliary fistula established for the treatment of a chronic hepatocholangitis. The case made possible not only the study of the possible choleretic effect of sodium nicotinate and nicotinamide, but also the correlation of the changes in serum bilirubin level with those of the bile concentration of bilirubin, following the administration of the drugs. The serum total and direct reacting bilirubin and the bile bilirubin level were followed at one-hour intervals for eight hours after the intravenous injection of 30 mgs. of sodium nicotinate, and then again after 24 and 48 hours. Serum bilirubin and bilirubin concentration in the fistula bile were determined with the methods of Jendrassik and Grof (5,4). The analytical results are presented in Table I. They indicate that the injection of sodium nicotinate was followed by stimulation of the biliary excretion of bilirubin, still moderately evident after 48 hours. Also the concentration of biliary salts in the bile (determined with the method of Cottet, 2) was moderately increased from the fourth to the eighth hour of the experiment.

After a 4 week rest, the same patient was given 300 mgs. of nicotinamide intramuscularly for a period of 15 days. Concentration of bilirubin in the bile, fecal and urinary urobilinogen, urinary bilirubin and serum bilirubin were followed at the same time. Urinary bilirubin was determined with the quantitative method of Jendrassik and Grof (4) and fecal and urinary urobilinogen with the method of Watson (12). The results show that, while the bilirubin level in serum decreased slightly, the excretion of pigments through the bile fistula and in the feces increased rapidly during the early phase of the treatment. During the second week of therapy, however, all values slowly returned to the original ones (Table 2).

DISCUSSION

The results presented in this paper show that sodium nicotinate and nicotinamide, given either intravenously or orally, possess cholagogic action. In case of retention of biliary pigments a choleretic effect can also be demonstrated.

The significance of these results in the study of the metabolism of the biliary pigments has been commented in a previous communication (10). It may be added here that the present findings seem to support the observations of Villa (11), who claimed that treatment with nicotinic acid and nicotinamide produced a striking remission of jaundice in different types of hepatic dysfunction with "reversible" liver damage. No resolutive therapeutic effect was observed in cases with severe impairment of the function of the liver. Villa's findings have been confirmed by other authors (1,9,3,8). In the case under observation, a single intravenous injection of sodium nicotinate and continued treatment with nicotinamide temporarily increased the excretion of bile pigments, at the same time lowering the bilirubin level of serum. They failed, however, to influence favorably the further course of the condition, as could have been expected due to the serious impairment of liver function.

SUMMARY

Sodium nicotinate and nicotinamide, given both orally and parenterally, possess an evident cholagogic effect in healthy subjects. A temporary cholagogic and choleretic effect with decrease of the serum bilirubin level was observed in a patient with severe jaundice presenting a biliary fistula established surgically for the treatment of chronic hepatocholangitis.

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ANTI-ANEMIC AGENTS AND CHOLINESTERASE ACTIVITY*

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EVIDENCE is accumulating which indicates that cholinesterase activity may be vitally concerned with etiology of pernicious anemia, as well as with the induced therapeutic remission of this condition. Sabine (1) has shown that the cholinesterase activity of the red blood cells is low in human macrocytic anemias, and rapidly increases early in the course of therapeutic remission. Meyer et al (2) have confirmed this work. We have reported various experiments (3,4) which show that both liver extract and pteroylglutamic acid are capable of activating the serum cholinesterase. In addition, it has been demonstrated (5,6) that the daily adminstration of choline or acetylcholine to dogs, under the conditions of our experiment, is capable of producing a hyperchromic anemia in which therapeutic remission may be induced by liver injection, pteroylglutamic acid, or atropine sulfate. We have also presented evidence (7) that the serum acetylcholine concentration is high in human pernicious anemia during relapse, but is diminished to the normal range by effective treatment early in the course of therapeutic remission. Finally, Barnard (8) has reported an early incipient hematologic response in pernicious anemia patients as the result of the injection of a cholinesterase-rich human plasma globulin fraction (IV-6).

The investigation herein described was made in the effort to learn more about the relationship between cholinesterase activity and folic acid or liver extract.

Method: Ten milligrams of powdered liver[1] (prepared at 40° C or lower) was mixed with water and either 0.1 unit of liver extract[2] of 1 mgm of folic acid[3]. The total volume of liquid was 2 cc. The mixture was incubated to 37° to 40° C for 3 hours, with occasional shaking or agitation. Control mixtures of powdered liver in water were incubated simultaneously with the test mixtures. The cholinesterase activity of each mixture was then estimated by an electrometric titration method which has been described previously (3). Each mixture, after incubation, was added directly to 25 cc of the substrate solution. Acetylcholine bromide and methacholine chloride were used as substrates in different tests. The concentration of substrate was usually 0.02 M, although in some tests it was .003 M. Generally similar results were obtained with each concentration.

Results: Table 1 lists the cholinesterase activities of the various incubated mixtures as measured by hydrolysis of the two substrates. The enzyme activities are listed in terms of cc of 0.01 N sodium hydroxide required to neutralize the acetic acid liberated by the mixture in a solution of acetylcholine (or mecholyl) in 10 minutes at a constant pH of 7.38 and at room temperature.

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1 Viobin "Liver 40"

2 Winthrop's "Campolon."

3 "Folvite" was generously supplied by Lederle Laboratories.

EFFECT OF LIVER EXTRACT AND FOLIC ACID ON CHOLINESTERASE ACTIVITY*

Substrate: acetylcholine bromide				Substrate: Mecholyl Chloride			
control	F. A.	control	L. E.	control	F. A.	control	L. E.
.02	.15	.02	.15	.02	.07	.02	.18
.08	.30	.08	.25	.03	.08	.00	.33
.09	.21	.08	.28	.00	.00	.02	.14
.03	.19	.01	.18	.00	.10	.00	.29
.00	.24	.02	.19	.02	.05	.02	.25
.00	.11	.00	.09	.02	.05	.02	.15
.00	.12	.00	.08	.02	.08	.02	.25
.00	.10	.04	.16	.02	.06	.02	.35
.04	.25	.04	.23	.00	.06	.00	.31
.01	.22	.01	.22	.00	.03	.00	.16
Av .027	.19	.03	.183	.013	.048	.012	.251

*In terms of cc of 0.01 N Sodium hydroxide required to neutralize the acetic acid liberated by hydrolysis of the substrate during a 10 minute period.

In the columns under the heading "control," are listed the enzyme activities determined after incubation of powdered liver alone in water. It will be seen that negligible cholinesterase activity was contained in the control mixtures. The second and fourth columns indicate that the addition of either folic acid or liver extract caused significant increases of cholinesterase activity, which in either case approximate a 6-fold increase over the control values. Such were the results when acetylcholine was used as the substrate.

The sixth and eighth columns show the activities produced by incubation of folic acid and liver extract, respectively, with powdered liver, when measured with mecholyl as the substrate. In this case folic acid produced only a 4-fold increase of enzyme activity, while the liver extract produced a 20-fold increase in the initial hydrolysis rate of mecholyl. Neither folic acid nor liver extract, when used alone, produced any hydrolysis of the substrates.

DISCUSSION

It appears from this study that, under the conditions of our experiment, liver extract activates particularly a *specific* type of cholinesterase, which is capable of hydrolyzing mecholyl as well as acetylcholine. On the other hand pteroylglutamic acid appears to increase principally the activity of a *non-specific* cholinesterase which will hydrolyze acetylcholine, but not acetyl B-methyl choline (mecholyl).

It seems to be well established, clinically, that liver extract injections will arrest the neurological manifestations of pernicious anemia, whereas pteroylglutamic acid will not. If cholinesterase regeneration is causative or important as a factor in the therapeutic remission of this disease, our experiments tend to afford an explanation of the difference in the therapeutic actions of liver extract and folic acid. Liver extract seems to increase mainly a type of *specific cholinesterase* which is the general type found in the central nervous system, while pteroylglutamic acid increases especially a *non-specific* esterase of the general type found in human blood serum.

CONCLUSIONS

The incubation of powdered liver with injectable liver extract caused an activation, or perhaps formation, of a cholinesterase which had some of the properties of a specific cholinesterase. This was, in general, of the type found in red blood cells and in the central nervous system.

The incubation of powdered liver with pteroylglutamic acid activated, or created, mainly an activity which resembled that of a non-specific cholinesterase of the general type that is found in blood serum.

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CHLOROMYCETIN AND AUREOMYCIN IN PROCTOLOGY

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INTRODUCTION

IN A previous paper I have detailed the proctologic applications of the sulfonamides and the newer antibiotics, with the exception of chloromycetin and aureomycin. At the time of the initial writing these latter antibiotics had not yet been adequately evaluated in my own practice, or generally. Their increasing importance in the proctologic armamentarium is now more evident.

Indeed, in the treatment of coccal infections it may well be that aureomycin will replace penicillin and the sulfonamides. Streptomycin continues preeminent in the therapy of tuberculous lesions, but aureomycin is perhaps superior in control of other bacillary infections.

In the preparation of the patient for intestinal surgery aureomycin has proven practical. Its value has also been demonstrated in the treatment of chronic non-specific ulcerative colitis. Chloromycetin may also be employed for sterilization of the gastro-intestinal tract either pre-operatively or post-operatively.

Chloromycetin seems to be of value in Salmonella infections, and there is some suggestion that it may prove itself in Shigella dysentery. Further study is required, however, in Shigellosis.

Clinical cure in lymphogranuloma venereum has followed adequate dosage with chloromycetin. Similar action has been observed in granuloma inguinale. Aureomycin has also proven useful in both conditions. Chloromycetin orally in granuloma inguinale is definitely advantageous over streptomycin parenterally. There is some evidence that chloromycetin may be of value in the therapy of luetic rectal and perianal lesions.

AUREOMYCIN

The discovery of aureomycin is the result of the work of B. M. Duggar of the Lederle Laboratories, and his late colleague, Dr. Y. SubbaRow, who directed this work until his death. Aureomycin is derived from a hitherto undescribed species of the Actinomycetes, the Streptomyces aureofaciens. The name is derived from the golden yellow color of the product.

The antibiotic seems effective in the therapy of many Gram negative and Gram positive bacterial infections, including streptomycin-resistant and penicillin-resistant organisms. On a weight basis aureomycin would appear to be less effective than penicillin against coccal infections. A very great advantage, however, lies in the fact that aureomycin therapy does not result in any marked development of bacterial resistance, even after prolonged therapy. This is in marked contrast with penicillin.

Aureomycin may be effectively employed in the pre-operative preparation of patients. Its action in this therapy is apparently more rapid than that of the insoluble sulfonamides such as sulfaguanidine and sulfasuxidine. However, there are conflicting reports in this direction, and further work is required for final evaluation of relative merit.

The marked antibiotic effect of aureomycin against Escherichia coli and other intestinal flora suggested its use in non-specific ulcerative colitis. An oral dosage of one to two grams daily (in divided doses) usually results in a reduction of the number of stools and a disappearance of blood from the stool. Aureomycin has been employed in the treatment of severe pyoderma gangrenosum complicating intractable non-specific ulcerative colitis. Small doses, (20 mg. dissolved in 2 cc. of saline) were given intramuscularly daily. The skin lesions healed rapidly, and the drainage of blood and pus from the distal ileostomy stoma and from the rectum ceased.

Aureomycin has been employed in the therapy of Salmonella infections. An insufficient number of cases, however, make it impossible to offer a final evaluation.

Endamoeba histolytica infections have also been treated with aureomycin. Again, the results are interesting and suggestive, but a larger series of cases, with adequate follow-up examinations after treatment, are essential for proper evaluation.

Streptomycin-resistant granuloma inguinale patients have been treated successfully with aureomycin. Indeed, the response to oral aureomycin is dramatic in

such cases. Four such cases have been reported by Greenblatt and his group, and the ideal dosage is suggested to be between five thousand and fourteen thousand milligrams, administered in capsules of two hundred and fifty milligrams each four times daily.

Successful aureomycin therapy has also been described in lymphogranuloma venereum patients. Intramuscular administration of twenty milligram doses dissolved in two cc. of isotonic sodium chloride has been recommended, the daily dosage ranging from ten to forty milligrams. Rapid reduction in size of inguinal bubos was observed. Decided improvement was also noted in lymphogranuloma venereum proctitis. Evidences of improvement were seen both symptomatically and upon proctoscopic examination. Improvement was also observed in patients with long standing lymphogranulomatous rectal stricture. A decrease in rectal discharge and bleeding was reported in many cases, and some increase in diameter of stool was noted as early as the fifth day after the beginning of treatment. Some cases, however, showed no change in the rectal stricture.

Aureomycin appears to be non-toxic whether given orally or parenterally. Occasional mild diarrhea and nausea is observed but is of little consequence. The usual dosage is five hundred milligrams (two capsules) every six hours the first day, followed by a maintenance dose of two hundred fifty milligrams every six hours. If the patient cannot swallow capsules, or if parenteral administration is deemed necessary, an intravenous dosage of two hundred to one thousand milligrams dissolved in five hundred cc. of five per cent glucose in distilled water may be given over a one hour period.

CHLOROMYCETIN

Chloromycetin is a crystalline antibiotic isolated by Ehrlich and his co-workers at the Parke, Davis & Company Laboratories. The initial product was obtained from a new species of soil organism, from field soil collected in Venezuela. The mold was designated as streptomyces venezuelae. Chloromycetin is the first antibiotic to be produced synthetically in sufficient quantity, and with sufficient facility, to be of commercial practical value. The name is derived from the high content of non-ionic chlorine in the molecule.

In general we may say that chloromycetin is well utilized orally, and is well tolerated. It may even be employed rectally in infants and children.

Chloromycetin seems to be of value in the subacute and chronic stages of ulcerative colitis. The action is apparently due to its bacteriostatic effect on the streptococcal and colon groups of organisms. A dosage of 3.0 grams of chloromycetin daily (in divided doses) has inhibited intestinal flora in these cases. However, more extensive clinical trial is important for full evalution.

Salmonella infection and specific Shigella dysentery have been experimentally treated with chloromycetin. The Salmonella Oranienberg, Newport, San Diego, typhimurium, and cholerasuis, have been eliminated from the stool after two to five days of therapy with fifty to seventy-five milligrams per kilogram of body weight in divided daily doses at three to six hour intervals. Again, further observation is essential for clinical evaluation.

The use of chloromycetin is also suggested in gonococcal proctitis. There is reason for clinical optimism, and the effective dosage appears to be 3.0 grams initially, followed by 1.0 gram every eight hours for two or three days.

Even more optimism is demonstrated by those who have employed chloromycetin therapy in lymphogranuloma venereum. A dosage of 3.0 grams every eight hours for fourteen days has proven effective in many instances.

Granuloma inguinale patients respond well to chloromycetin. A total dosage of twenty grams, administered in individual doses of 0.5 gram to 1 gram four times daily for five to ten days is required. The major advantage over streptomycin lies in the fact that chloromycetin may be taken orally. If examination of the tissue for Donovan bodies is still positive after seven days of therapy, the antibiotic should be continued until healing is complete. The dosage range may be from twenty to forty grams, and the average time required may be as long as twelve days.

Luetic proctitis and perianal lesions are under experimental therapy with chloromycetin. It is too early to evaluate clinical results.

CONCLUSION

Aureomycin and chloromycetin increase the range of antibiotic therapy in proctology. The use of aureomycin for pre-operative preparation appears encouraging. However, there are conflicting reports.

Both aureomycin and chloromycetin have been employed in the treatment of chronic non-specific ulcerative colitis. Again, the results are encouraging but not specific. The same may be said for the therapy of Salmonella infections.

There is also suggestive (but not final) evidence to indicate favorable results in the use of aureomycin for the therapy of Endamoeba histolytica infections.

Aureomycin has been most successful in the treatment of streptomycin-resistant granuloma inguinale patients. These patients also respond well to chloromycetin. Either aureomycin or chloromycetin may be taken orally, and this is a major advantage over streptomycin therapy.

Both aureomycin and chloromycetin have demonstrated their value in lymphogranuloma venereum patients. Evidences of improvement are seen both symptomatically and upon proctoscopic examination.

Chloromycetin has also been employed in gonococcal proctitis and in luetic lesions. However, clinical evaluation is not yet complete.

In general we may say that both antibiotics are well utilized orally, and well tolerated.

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TEN CASES OF AMOEBIASIS WITH ARTHRITIC COMPLAINTS*

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PRIOR to the second World War a systematic search for intestinal protozoa in patients of the continental U. S. A. was pursued only by a few workers, and then mostly in the Southern States. Surveys, according to which the incidence of amoebic infection in man was estimated at 10% of the total population, led to the assumption that the majority of these infected individuals had to be symptomless carriers rather than to a re-evaluation of clinical symptoms and laboratory findings.

Even at this time the average laboratory technician is rarely qualified to examine stools competently for protozoans. Those who have dedicated their attention to intestinal parasites for years, have been rewarded by gratifying results, and as time has gone on they have become acquainted with the symptomatology of chronic amoebiasis. As this information increased the incidence of theretofore "asymptomatic carriers" diminished in reversed ratio.

Craig and Faust (1) believe there is no such thing as a healthy carrier; since at autopsy one usually is able to demonstrate the finding of typical small ulcerations in the mucosa of the large bowel of known "carriers" of Endamoeba Histolytica. In the chronic stage of the disease, Endamoeba Histolytica is found in the lumen as well as in the mucosal ulcerations of the ascending colon and cecum. So long as such an infection does not extend beyond the splenic flexure the clinical picture of an acute dysentery is not encountered. Hence, the sigmoidoscope is of value only in the acute stage of amoebiasis, the amoebic dysentery.

If we exclude serious complications such as abscesses of the liver or the brain, the common symptoms of chronic amoebiasis are:

1. Spastic constipation, 2. Alternating diarrhea and constipation, 3. Frequent eructations and "gas on the stomach," 4. Vague abdominal discomfort, 5. Nausea, particularly in the early morning hours, 6. Loss of appetite, 7. Fatigue and lightheadedness, 8. Loss of weight, 9. Pain in the right lower abdomen, usually located at McBurney's point. However, there usually is no rigidity of the abdominal muscles and a non-committal white blood cell count. In such cases, the presence of gurgling of the cecum on palpation is of important help in the differential diagnosis of appendicitis. If it is present, the patient probably does not have appendicitis, 10. Hepatitis with hepatic enlargement, tenderness of the liver-edge and fever, usually without jaundice, 11. Myalgia, rheumatic complaints and even rheumatoid arthritis are possible symptoms or complications, of chronic amoebiasis, due to E. Histolytica. Several authors believed that this protozoan could be demonstrated in the synovial membranes of arthritic joints, however, it appears now that these authors have been victims of deceptive cytologic similarities between E. Histolytica and certain physiologic human cells.

The speculation as to an association of arthritis and rheumatic complaints and symptoms with intestinal abnormalities (2,3) or infections (4,5,6,7,8,9,10,11) and in particular with parasitic infections of the intestine (12,13,14,15,16) appeared early in the medical literature and never has entirely disappeared from our current references. Authors previously have ventured to point out that strains of streptococci in the colon might well represent the sensitizing bacterial invaders in many cases of rheumatoid arthritis. Since the same strains of bacteria can be cultured from the bowel of arthritics as well as from apparently healthy individuals it had to be assumed that an added influence was instrumental

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TABLE

	Case # 1.	Case # 2.	Case # 3.	Case # 4.	Case # 5.	Case # 6.	Case # 7.	Case # 8	Case # 9	Case # 10
Age	60	42	48	41	42	40	58	28	28	29
Sex	F	F	F	F	F	F	M	F	F	F
Symptoms and physical findings.	Fatigue, backache, headache, loss of weight.	Fatigue, pain in chest & back, headache, loss of weight, nausea, pain in lower abdomen.	Fatigue, chest-pain, loss of weight, nausea, general swelling, stiffness & extreme pain in joints.	Pain in neck, pain in lower abdomen, loss of weight, liver enlarged & tender, Fever (99-100°F) Diarrhea.	Headache, swelling & pain in fingers, low-grade fever (100)	Fatigue, pain in shoulders & neck. Pain in lower abdomen. Radicular pain in chest.	Fatigue, pain in lower abdomen & shoulder, loss of weight, liver enlarged and tender to palpation.	Fatigue, pain in back and shoulders. Pain in lower abdomen, occasional diarrhea. Radicular pain from 3rd to 5th ICS, at left sternal margin.	Fatigue, backache, pain in lower abdomen, liver edge palpable, nausea, mucous in stools.	Fatigue, backache, pain in the back of the neck, pain in lower abdomen, liver edge palpable, tender, pain in joints.
Previous surgery	-	Appendectomy & rt. oophorectomy	Appendectomy	Appendectomy		Appendectomy & Rt. Oophorectomy		-	Appendectomy	Hysterectomy, removal of hepatic adenoma.
Duration of arthritis	6 months	6 months	5 months	1 years	4 years	4 years	3 months	7 months	3 years	1 year
Symptoms referring to abnormalities	-	Mod. hypothyroidism	-	-	-	-	-	Hypothyroidism	-	Climacterium
Pat. Rate.	4.6 mm/hr	4 mm/hr	14 mm/hr					24 mm/hr	12 mm/hr	14 mm/hr
C.B.C.	Hb 12. gms RBC 3.140000 WBC 6050 Eosin. 0%	Hb 11. gms RBC 3.760000 WBC 6300 Eosin. 1%	Hb 12.5 gms RBC 3.900000 WBC 7,800 Eosin. 0%	3 mm/hr Hb 10. gms RBC 3.900000 WBC 6300 Eosin. 0%	10 mm/hr Hb 10. gms RBC 3.760000 WBC 6300 Eosin. 0%	8 mm/hr Hb 10.5 gms RBC 3.960000 WBC 4400 Eosin. 4%	7 mm/hr Hb 14. gms RBC 4.880000 WBC 9700 Eosin. 0%	24 mm/hr Hb 12.8 gms RBC 4.090000 WBC 7700 Eosin. 7 %	12 mm/hr Hb 11. gms RBC 3.900000 WBC 6000 Eosin 0	14 mm/hr Hb 9.6 gms RBC 3.760000 WBC 7750 Eosin 7 %
Spine-tenderness.	C_6-T_1	C_1-C_5 D_9-D_{11}	C_3 - C_7 D_1- D_5	C_3 - C_7	T_4 - C_7 L_1 - L_5	C_7 D_1 -D_5		C_4 - C_8 D^4 - D^8 5	D_4 - D_8	C_4 - C_8
Large Joints	-	-	Both shoulder & elbow-joints swollen, painful, very limited excursion, tenderness of injured joints.	-	Tenderness over both sacroiliac joints.	-	Left shoulder joint painful on abduction & external rotation.	-	-	Stiffness and crepitation of both knee joints.
Small Joints	Crepitation On posteroflexion Of C_6 - C_7	-	Swelling & tenderness of 1st interphalangeal joints of all fingers.	-	Swelling of 1st interphalangeal articulations	-		-	-	Spindling of proximal interphalangeal joints. Crepitation upper cary. spine.
Muscle spasm	Trapezius & post. nuchal muscles	Trapezius and posterior nuchal muscles	Trapezius & posterior nuchal muscles, flexors of both arms	Trapezius & posterior nuchal muscles.	Trapezius lumbar portion of erector trunci.	Trapezius	-	Trapezius, posterior nuchal muscles, lumber portion of erector trunci.	Erector trunci of the middorsal portion.	-
Muscle atrophy	-	-	Interossei of both hands	-	-	-	-	-	-	-
Intestinal Parasites	E. Histolytica	E. Histolytica	Giardia Lamblia E. Histolytica	E. Histolytica E. Coli	E. Histolytica	E. Histolytica	E. Histolytica	Chilomastix Mesnili E. Histolytica.	E. Histolytica	E.Histolytica
Therapeutic agents	Carbarsone Diodoquin added proteins 10 gms	Emetine, Carbarsone Diodoquin, Thyroid extract, added proteins to diet.	Carbarsone, Diodoquin Atabrine, added proteins to diet.	Carbarsone Diodoquin Emetine HCl.	Carbarsone Diodoquin	Carbarsone Diodoquin	Carbarsone Diodoquin	Carbarsone Diodoquin Thyroid extract	Emetine HCl Diodoquin	Emetine HCl Carbarsone Diodoquin
Progress in two subsequent years.	After 2 months all above symptoms had disappeared, including crepitation & muscle spasm. After 2 years none of the above complaints had recurred.	After 2 months pain in chest & back disappeared, appearance of reticular pain and muscle spasm. After 2 years no complaints.	After 2 months all pain in weight, disappeared weight, all joints greatly improved as to motion and pain. After 2 years disappearance of muscle-atrophies, pt. feels well with exception of stiffness in her left shoulder after exercise.	No drop in temperature until Emetine-HCl was administered, then after 4 months disappearance of fever, pain, muscle spasm, diarrhea. Liver no longer palpable, gain in weight. After 3 years no return of symptoms.	After 4 months gone improvement of fingers. After 11 months no more headache or joint pain. After 2 years no recurrence of symptoms.	Symptoms and disappeared after 7 months and had not recurred after 2 years.	After 3 months no complaints. No recurrence after 2 years.	After 2 months improvement of muscular pain and disappearance of abdominal symptoms.- After 14 months disappearance of muscular pain. After 4 years no recurrence of symptoms.	After 10 months some headache after heavy physical exertion. No more fatigue or abdominal symptoms. After two years no recurrence of symptoms.	After 4 months dramatic improvement of all symptoms, some stiffness remains in knees. After 2 years no recurrence of symptoms.

either to promote an increased virulence of the bacterial flora or in sensitizing the host (4).

The presence of mucosal ulcerations due to E. Histolytica in the large intestine might possibly be instrumental in opening avenues of invasion to the bacterial intestinal flora. This, of course, would presume the theory of bacterial sensitization as etiology of rheumatoid arthritis to be correct and established.

The following ten cases represent infections with E. Histolytica in which existing myalgias or arthritic complaints and findings were dramatically improved by amoebicidal therapy. No attempt is made to interpret these results as proof for or against any of the existing theories of the etiology of rheumatoid arthritis or its associated lesions. Many agents exert beneficial influence on the course of this group of diseases and an adequate dietary regime seems to be as helpful as any other single agent. Whether an infection with E. Histolytica represents a focus of infection or an adjuvant to bacterial invasion, or whether it merely interferes with the food absorption or other physiologic mechanisms, its presence seems to aggravate an existing arthritis and its elimination frequently improves the clinical symptoms and findings.

For the sake of clarity and brevity, these ten cases are presented in the form of a table. Chemical examinations of the blood and roentgenological examinations of the joints were performed in only some of these cases, and since under these circumstances they are of no value for comparison, they were omitted from the table. Of other laboratory and clinical findings, only those of direct significance were retained in the table. Two negative stool examinations within six months after the original positive findings were deemed sufficient to pronounce the patient cured of his amoebic infection.

A few interesting figures emerge from the above table: The average age of the patients was 45.9 years, eight were females, two males. The most frequent symptoms at the time of their first examination were fatigue (8 cases), backache and chest pain (7 cases), occipital head and neckache (6 cases), due to spasm of the posterior neck muscles. Tenderness and pain in the lower abdomen ranks next with the incidence of five cases. In this connection it may be interesting to remember that five patients had appendectomies, two of them also right oophorectomies. Four of these individuals still had the same abdominal tenderness and pain which led to their operations in the first place, but lost it after completed amoebicidal therapy. Five patients had lost weight and regained it after therapy.

The red blood cell count was not at all characteristic with a rather fair average of 3,920,000 and Hemoglobin of 11.4 grams per 100 cc. The eosinophile leukocytes were increased beyond normal limits in only three cases, two of which represented mixed infections with mastigophora, one with Chilomastix Mesnili, the other with Giardi Lamblia. The remaining cases showed from none to 4% eosinophile leukocytes.

Arthritic involvement was most predominant in the spine as expressed in segmental spinal tenderness, muscle spasm and radicular neuralgia, the latter particularly in the intercostal spaces adjacent to the sternal borders. With the incidence of eight cases, the cervical portion of the spine was by far the most frequent seat of these changes. Four cases presented involvement of the larger joints, in one case to a crippling extent. Four other cases showed arthritic involvement of the interphalangeal articulations. Three cases of the ten definitely can be classified as rheumatoid arthritis. All ten cases were infected with Endamoeba Histolytica, three of them representing mixed infections with Endamoeba Coli, Chilomastix Mesnili and Giardia Lamblia. Subsequent courses of Carbarsone and Diodoquin were employed in the therapy of every case. A course of Carbarsone consisted in the administration of 0.75 gms. daily for seven days; whereas, Diodoquin was given at a daily dose of 1.8 gms. for three weeks. Emetine Hydrochloride was used in conjunction with this therapy wherever an enlargement of the liver, or an elevation of the temperature was present. In these cases, the presence of amoebic hepatitis was assumed and Emetine Hydrochloride was deemed to be more effective against trophozoites of E. Histolytica in tissues outside the intestinal tract than oral medication alone.

There was no failure of Emetine therapy in this small series. Whenever such a failure does occur the intravenous administration of Neoarsphenamine or Mapharsen is helpful.

CONCLUSION

In conclusion, it may be stated that in every case of rheumatoid arthritis, arthralgia or myalgia it seems well worth while to keep examining stools for protozoan parasites until their presence is either established or disproved. If present, their elimination is likely to be a valuable aid in our therapeutic efforts.

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IDIOPATHIC PNEUMOPERITONEUM
A REVIEW OF THE LITERATURE AND REPORT OF ONE CASE

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"SPONTANEOUS pneumoperitoneum" is defined by Mason, Mason, and Kesmodel (1) as the presence of free air in the peritoneal sac unassociated with any intentional procedure. The authors believe that the term idiopathic pneumoperitoneum would be more descriptive of the pneumoperitoneum of unknown etiology, in contrast to conditions such as perforating peptic ulcer, with associated spontaneous pneumoperitoneum. In such cases the etiology of the pneumoperitoneum is known and yet there are no intentional procedures related. Therefore it is believed that cases such as the one to be presented should not be classified in the same group as those following perforated ulcers, perforated viscera and other such cases of known etiology. There are several cases scattered throughout the European and American literature that are of undemonstrable etiology and are not associated with symptoms of peritonitis. In these cases and in the case discussed in this paper, no communication with the abdominal or thoracic viscera or with the exterior could be demonstrated.

The symptoms in most of these cases have been benign and diagnosis has been established by x-ray or paracenteses. With the increasing use of x-ray as a diagnostic aid, we expect many more such cases to be found and hope to offer the practitioner a brief summary of the associated lesions one might expect to find and the experiences of others in treatment.

Hinkle (2), in a review of the literature in 1940 found only two reported cases of "spontaneous pneumoperitoneum" unassociated with perforated viscus or peritonitis and added a third case. In September 1944, Sidel and Wolbarsht (3) reported a case, and in October 1944 Leys (4) reported three cases of "spontaneous pneumoperitoneum" in women, one postoperatively (fibroid), complicated by a right pleural effusion. There was no further discussion as to the specific pathological findings in this case. One was associated with an active duodenal ulcer and pyloric stenosis and a ptosis of the stomach, with symptoms of pyloric obstruction and bleeding. The third case was associated with intermittent abdominal pain and no organic lesion could be demonstrated. One year later this patient was admitted as a surgical emergency and was operated on at which time a large amount of free gas was released. Forty-eight hours later it was necessary to repeat this procedure because of a rapid re-accumulation of gas. The following day distention occurred again and aspiration of the gas was done with complete relief of symptoms. Following this procedure, she had one episode of similar pain two weeks later, which disappeared without treatment. Following this, there were no symptoms or x-ray evidence of any lesion of the gastro-intestinal tract or of any gas under the diaphragm.

In 1946 Mason, Mason and Kesmodel (1) reported one case of a white male who developed pneumonia and on the tenth day following therapy was noted to have an acute abdominal distention and discomfort without signs of peritonitis. At this time x-ray revealed the presence of an extensive pneumoperitoneum. The pneumonia was resolving and no demonstrable lesion of the gastro-intestinal tract was found. Twelve days later the pneumoperitoneum had diminished considerably and 102 days later the abdomen was negative. At a later date, the patient was seen again, complaining of abdominal distention, but no free air was observed.

There is one condition associated with pneumoperitoneum which has not been described in the recent English or American literature. As reported by Stenstrom (5) this is the condition known as pneumatosis cystoides intestinalis or emphysema bullosum intestinale. This condition was first described in swine in 1823 and first reported in the human by Bang, in 1816, being found in the course of an autopsy. In 1889 Hahn diagnosed the condition during a surgical procedure. In all there are some 150 cases of this disease recorded. It is characterized by the formation of many cysts ranging from the size of a pea to the size of a human fist. These are generally located on the small intestine but they have also been noted on the colon, stomach, diaphragm, omentum and have been found in associated lymph glands. The cysts are noted to be gas-filled, the composition of which is unlike that of any of the other gases of the intestinal tract. There are differences of opinion as to its physical properties, which question has not been settled to this time.

The microscopic picture is equally vague, the only positive findings being the presence of giant cells in the wall of the cyst.

There are two classifications of this condition. Primary pneumatosis—in which there is no associated intra-abdominal pathology and the secondary type which is associated with intra-abdominal pathology. This associated pathology, in most cases, is that of a juxtapyloric ulcer with a resulting stenosis. This is found in as high as 50% of all cases according to some authors. This finding together with x-ray findings of free gas under the diaphragm and free loops of bowels interposed between the liver and diaphragm are more than suggestive of an idiopathic pneumoperitoneum. The diagnosis may however be impossible for even at abdominal laparotomy the vesicles may have entirely disappeared. The residual may sometimes be noted as grayish-white plaques on the wall of the gut.

The etiology of the cysts varies according to the different authors. One theory is the mechanical which attributes the cysts to penetration of intestinal gas into

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the intestinal wall through minute lesions in the wall itself. The cause of the minute lesions is unknown. Others state the etiology to be on a bacterial or viral basis. One author advances the theory that the cysts are due to formation of gas by a "Bacterium Pneumatosis." This is described as a gas forming bacteria resembling the colon bacillus. We have been unable to find any description of this bacteria in the recent texts or by consultation with several bacteriologists.

CASE REPORT

The following case was observed at the North Little Rock, Arkansas, Veterans Administration Hospital from December 8, 1948, until March 16, 1949. Prior to date of hospitalization, the patient was examined October 5, 1948, for pension rating purposes on the basis of ulcer symptoms since 1921.

T. D., a 53 year old colored male was admitted to the hospital on December 8, 1948, with complaints of "stomach trouble and joint stiffness." He was in excellent health until 1921, when he first began having episodes of epigastric pain and flatulence. The epigastric pain was usually noted as occurring one to two hours after meals. It was described as being of a very severe nature, causing him to seek his bed for relief. The ingestion of large doses of sodium bicarbonate usually gave some relief. He was seen at this time by a private physician who placed him on a diet consisting of ham, eggs, and coffee. He ate little else for a period of about one year and received some measure of relief from this routine. He remained free of all symptoms until 1938, when he had an acute recurrence of the previous syndrome. At this time, the pain was more severe than on previous occasions, and, in addition, there was radiation of the pain into the left upper abdomen and into the infrascapular area. The epigastric pain now also occurred during the sleeping hours, usually being noted about midnight and lasting from one to two hours without abating. Nausea, vomiting, and vertigo were noted during these episodes. Occasional clay colored stools were noted during this period also.

In 1944, he was treated at another Veterans Administration Hospital where a diagnosis of peptic ulcer was made and he was treated accordingly, but without relief for one and one-half months. He then returned home and carried on his usual work as a bellhop, but continued to have intermittent recurrences of epigastric pain, as described above. Symptom review gave no additional information.

Physical examination revealed a well developed, well nourished, colored male, age 53, who was in no distress. Head, eyes, ears, nose and throat were within normal limits. There were numerous carious teeth. The heart tones were normal, no murmurs or bruits were heard. The heart size was within normal limits. The lungs were normal to inspection, palpation, percussion, and auscultation. The genitalia were entirely normal. The upper extremities showed a mild hypertrophic arthritis, generalized. The abdomen was normal throughout except for a generalized tenderness to palpation over the entire epigastrium and loss of liver dullness to percussion. Rectal examination revealed no abnormalities. The back was normal. Neurological examination showed essentially normal reflexes throughout. No pathological reflexes were noted.

Laboratory findings showed a normal blood count and differential on admission, and a normal urinalysis, with a specific gravity of 1.030. The Kahn was 4 plus and 12 Kahn units and 8 Kolmer units positive. On a repeat examination, the Kahn was 3 plus and the Wassermann negative. A repeat blood count on February 4, 1949, was normal, and a complete urinalysis on that date was negative.

He had very few symptoms during his hospitalization. He was treated with a Sippy diet, tincture of belladonna and aspogen (aluminum hydroxide compound) tablets, without alteration in his complaints.

This patient was first referred to the x-ray department on December 9, 1948, for routine chest film and for gastro-intestinal studies.

The initial chest examination revealed a large accumulation of air beneath both leaves of the diaphragm. It was felt that there were haustral markings present, indicating that this air was within the colon and there was an interposition of the colon. Further studies, consisting of fluoroscopic examination of the chest and the abdomen, routine gastro-intestinal studies and barium enema studies, both separately and combined at a single sitting, revealed that these markings only represented a marked scalloping of the diaphragm, bilaterally, and that the air was free within the peritoneal space.

A study of the upper gastro-intestinal tract revealed a tremendous dilatation of the stomach with a marked retention of fluid in the stomach at the outset of the examination. The duodenal bulb was not adequately visualized at this time. Although his stomach was aspirated continuously and repeatedly, we were never able to obtain a "dry stomach." However, two satisfactory upper gastro-intestinal and two satisfactory colon studies were performed. The duodenal bulb was visualized and showed some deformity, indicating a chronically diseased bulb. There was no evidence of active ulceration or perforation, and there was no other demonstrable organic lesion of the gastro-intestinal tract. The stomach remained enlarged and hypotonic. There was 70 to 75 per cent retention in the stomach at the end of six hours, but the 24 hour studies revealed the barium to be in the colon.

At the time of discovery of the free gas it was contemplated that some of the gas would be aspirated and analyzed but the patient would not permit this procedure to be carried out.

During the three months this patient was hospitalized, the amount of air within the peritoneal cavity was seen to remain constant. It shifted freely from side to side, depending upon the patient's position. After a 30 day leave of absence, he was seen on March 16, 1949, for the last time and an abdominal scout film revealed no evidence of pneumoperitoneum. He was then discharged from the hospital as having received maximum hospital benefits.

SUMMARY

We have reviewed the literature with regard to the etiology of idiopathic pneumoperitoneum and have added the case of a 53 year old male with a history of symptoms referable to the gastrointestinal tract for the past 27 years. X-ray examination revealed the presence of free air beneath both leaves of the diaphragm with no

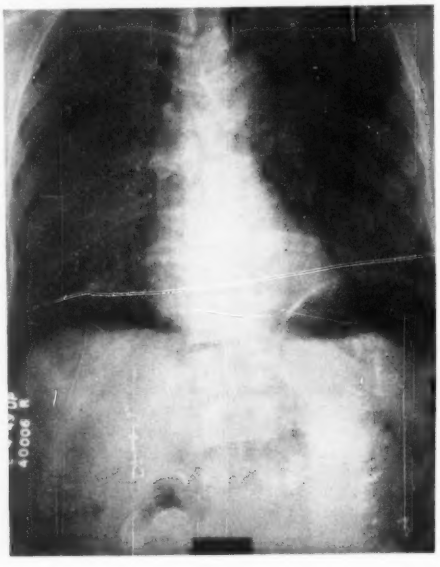

Fig. 1: Film taken at time of gastro-intestinal studies showing the barium filled stomach and the large accumulation of free air in the peritoneal cavity. The hepatic flexure and part of the splenic flexure are also shown. This film was made in expiration, hence the scalloping of the diaphragm is not present.

demonstrable acute lesion of the GI tract. A 70% gastric retention at six hours and some old deformation of the duodenal bulb were the only positive findings. Some three months after the initial hospitalization the patient was again x-rayed and there was no evidence of free gas in the abdominal cavity.

Study of the British and American literature for the past twenty years would lead one to believe this an infrequently found condition. The foreign literature, however, suggest that there are many cases, the etiology of many of which is probably due to a cystic disease of the intestinal tract known as pneumotosis cystoides intestinalis. This pathology should be sought for more closely by the surgeon and pathologist in order to better determine the true etiology of idiopathic pneumoperitoneum.

Acknowledgement is made to Dr. James R. Hughes, Chief, Medical Service, and to the various consultants at the Veterans Administration hospital, North Little Rock, Arkansas, who studied this case with us.

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NUTRITION NOTES

FOOD IN 1950

Supplies of food available to civilians in the United States are expected to continue at about the same high level as in the past two years. Even if the Korean situation results in some increase in military procurement of food in coming months, supplies available for civilians would not be noticeably affected.

Production of food this year is expected to total about the same as in 1949, 38 percent more than the 1935-39 average and 20 percent above 1941. Stocks of most foods which can be stored are fairly substantial. Furthermore, exports of food have been and are expected to continue smaller than during the past several years. On the basis of these supply estimates, civilian consumption of food per person this year is expected to average 11 percent higher than the 1935-39 average and a little above 1941, the record year before World War II.

Overall demand for food has strengthened this spring and summer along with the general rise in economic activity. The principal effect of the Korean situation on the food outlook for the next six months is likely to be the strengthening of consumer demand as employment and consumer incomes rise with the impact of an accelerated defense program. Through the first half of this year, military procurement of most foods for troop use and civilian feeding in occupied areas was at a lower level than in the same period of 1949. Although mobilization will be stepped up, military purchases are not expected to have a substantial effect on the overall demand for food products this year.

Prospects for food supplies and consumer and military demand point to slightly higher retail prices for food, but in the next 5 months prices are not likely to go more than 3 or 4 per cent above the July level. There has apparently been some speculative buying and price increases in food in recent weeks substantially similar to those occurring in 1939, which receded as soon as consumers realized that food supplies were adequate. The current food supply situation is again such that speculative buying and price increases are not warranted.

The supply situation for most livestock products is at least as favorable as last year and somewhat better than in the years before World War II. Although current indications are that both the wheat and corn crops may be about 200 million bushels short of 1949 crops, carryover stocks are very large and supplies of cereal food products for the coming year will be plentiful. Fruit crops are smaller than last year, largely due to unfavorable weather last winter for citrus and this spring for peach and pear crops, in particular. However, fairly large stocks of processed fruits and vegetables are available from the 1949 packs and the 1950 packs probably will be about equal to last year's.

Although the general level of food consumption per capita is expected to continue about the same as in 1949, for the year as a whole there may be some increase in the consumption of pork, poultry and eggs, frozen vegetables, sweetpotatoes, vegetable oil products and sugar. On the other hand, the consumption of beef and veal, fresh fruits and butter may be down slightly.

The increase in overall food consumption per person from the 1935-39 average level has resulted principally from higher consumption of livestock products except butter, processed fruits and vegetables, and vegetable oils. These increases have more than counter-balanced lower consumption rates for potatoes and sweetpotatoes, butter, fresh fruits, wheat and rye flour, and corn meal. Similarly, food consumption in 1950 is expected to average a little above 1941, the record prewar year, because of minor increases in dairy products and fats and oils except butter, and substantial increases in the consumption of poultry and eggs, canned and frozen fruit juices, frozen fruits and vegetables. The average rates of consumption of some foods in 1950 may be lower than in 1941—particularly canned fish, fresh fruits, potatoes and sweetpotatoes, sugar, wheat flour, and corn meal.

The current rates of food consumption per capita are somewhat lower than those attained at the end of the war, chiefly due to declines in the consumption of fluid milk and cream, ice cream, meats, fresh and processed fruits and vegetables. However, feed supplies are plentiful so hogs could be fed to heavier weights and the production of grain fed beef increased. The number of cattle on feed on July 1 in 11 Corn Belt States was 34 percent greater than a year earlier. The current dairy situation is such that increased supplies of fluid milk could be marketed upon demand. Similarly the packs of some canned fruits and vegetables could still be increased to meet stronger demand.

On the basis of present indications of food supplies and consumer demand, retail food prices in 1950 are expected to average about the same as last year. Lower prices this year of such foods as poultry and eggs, potatoes, and fats and oils except butter may about offset possible increases from 1949 in the annual average price of meats, fresh fruits, corn products, and processed fruits. (The National Food Situation, U. S. Dept. Agriculture, July-Sept. '50.)

ABSTRACTS ON NUTRITION

KATZ, L. N., STAMLER, J., AND HORLICK, L.: *Cholesterol metabolism in health and disease: its relationship to arteriosclerosis.* (Amer. Practitioner, May 1950, 461-468).

Cholesterol is a key pathogenic factor in arteriosclerosis but many gaps in our knowledge of its metabolism exist. Only in the rabbit and chick, and perhaps in man, can atherosclerosis be produced with but slight hypercholesterolemia. Man, the chick and the duck all develop arteriosclerosis spontaneously. Thyroid extract reduces blood levels of cholesterol, but it ought not to be used in the treatment of arteriosclerosis. Obesity and atherogenesis go hand in hand, and hypophagic individuals seem less likely to develop this arterial disease. Restriction of cholesterol in the diet is no insurance against arteriosclerosis. Atherogenesis in man probably is a discontinuous process, and atheroma may undergo regression and healing. Diabetes mellitus is the most important clinical entity associated with disturbed lipid metabolism, hyperlipemia and hypercholesterolemia. The normal variation of total plasma cholesterol levels in man vary from 167 to 320 mg. per 100 c. c. The total body cholesterol is remarkably constant in any normal individual, and there is a continuous hemato-enterohepatic recirculation of this substance. The body can synthesize cholesterol even when none exists in the diet. Cholesterol is present in all cells of the body.

ABBIS, H. S. C. AND CURRIE, R. D.: *Hypercalcemia during vitamin D treatment of rheumatoid arthritis.* (Brit. Med. J., Apr. 15, 1950, 877-879).

Two cases of toxicity due to massive doses of vitamin D are described. The administration of very large doses is followed, though not invariably, by a significant rise in the serum calcium level and metastatic calcification may occur in the kidneys, arteries and elsewhere. Probably the results of treatment of arthritis do not warrant its use for this purpose. Where large doses of vitamin D are to be employed, a constant check on the level of *diffusible* serum calcium and on the renal function should be made. In most instances of poisoning, withdrawal of the drug is all that is necessary to obtain a reversal of the lesions produced.

HISSINK, L. A. G.: *The value of the protein hydrolysate capain ("Anaparon") in the treatment of traumatic shock.* (Med. J. Australia, Feb. 11, 1950, 187-193).

"Capain" is a casein hydrolysate prepared originally by Prof. R. Brinkman at Groningen, Holland, in 1943. It consists largely of polypeptids along with a fraction of free amino acids. It is produced by the action of papain on casein, and possesses considerable water-attracting power. Hissink notes that blood and plasma transfusions sometimes fail to overcome prolonged shock. The use of capain, however, was satisfactory in nearly every instance. It maintains its hydrophilic qualities long enough intravascularly to combat secondary shock successfully. On the battlefields, the intravenous injection of concentrated capain solution may have life-saving effects by delaying the secondary loss of fluid out of circulation. It also is economical. Blood and plasma are now restricted to special indications.

POULSEN, O.: *Tuberculosis and nutrition.* (Ugeskrift for Laeger, 112: 135-142, Feb., 1950).

Seventh Day Adventists living on an ovo-lacto-vegetarian diet with prohibition of pork, alcohol, spices and stimulants were investigated primarily with a view to cancer morbidity, but a significant incidental finding was an increased tuberculosis morbidity, particularly among women between the ages of 15 and 44. The disease occurred chiefly in persons who had been members of this religious community for many years. A large number of the cases had a rapid course, promptly fatal in adolescence. The diets, poor in fat, were probably actually poor in available first-class protein, so that the presumable cause of the increased tuberculosis incidence was not only insufficient calories but too little protein to support antibody production.

SALLAZ, E. J.: *The new vitamin "T" for atrophy and dystrophy in infants.* (International Health Bull. of League of Red Cross Societies, II, 1, 18).

A compound in the form of vitamins was extracted from termites in 1945 by Prof. W. Goetsch of the Graz University. His subsequent research indicated that this compound did not come from the termites themselves but from certain mushrooms and ferments on which they feed. He succeeded in extracting them direct, in particular from the *tactula utilis* under the name of "vitamin T Compound." Fed to insects, it resulted in marked growth and eventual gigantism. It appears to owe its effect to increasing the absorption of albumin. It is being used to offer new hope in many cases of infantile marasmus.

UNGLEY, C. C. AND THOMPSON, R. B.: *Vitamin B_{12} and folic acid in megaloblastic anemias of pregnancy and the puerperium.* (Brit Med. J., Apr. 22, 1950, 919-924).

PATEL, J. C. AND KOCHER, B. R.: *Vitamin B_{12} in macrocytic anemia pregnancy and the puerperium.* (Brit. Med. J., Apr. 22, 1950, 924-927). Editorial, Brit. Med. J., ditto, 948.

Ungley and Thompson report negative results in treating 6 cases of the megaloblastic anemia of pregnancy by means of vitamin B_{12} injections, but better, sometimes good results from the use of folic acid. These cases were in England. Patel and Kocher, on the other hand, had good results in treating 5 similar cases in Bombay, India, by injections of vitamin B_{12}. These papers appear in the same issue of the B. M. J. and an editorial attempts to explain these two apparently contradictory observations by the probability that the cases in India were examples of tropical megaloblastic anemia of the Wills type, usually considered to be due to an insufficiency of the extrinsic factor in the diet.

WALKER, W. J.: *Obesity as a problem in preventive medicine.* (U. S. Armed Forces Med. J., 1, 4, 393-402).

Walker states that the greatest problem in preventive medicine in the U. S. today is obesity. It has exceeded the combined total of the four next common causes for rejection on medical grounds of applicants for standard life insurance. In one study, 2.1 percent of men and 4 percent of women applying for life insurance were declined for *any* insurance for this reason. In treatment he believes caloric restriction is all important since hunger pain is no worse on a 400 calorie diet than on a 1400 calorie diet, and the results are much better. He does not use thyroid extract except in myxedema. He stresses the value of amphetamine in reducing appetite, where necessary. He states that cure of obesity reduces the incidence of heart disease, cerebral hemorrhage, cancer and diabetes.

BEAN, W. B.: *Control in research in human nutrition.* (Nutrition Reviews, 8, 4, 97-99).

Utopia in human nutrition research would entail a large number of subjects, homogenous as to genetic factors, on controlled diets handled by a large metabolic team doing balance studies, varying single or multiple factors at will against a known background of past dietary experience, controlling biosynthesis in the gut, subjective influences, conditioning disease and a host of other variables. Emotional factors alone may upset results. Interpretation of the placebo effects is subject to error. We do not know why such mechanical defects as intestinal shunts may be followed by pellagra, beri-beri, macrocytic or microcytic anemia, or, on the other hand, apparent health. Why does tryptophane relieve pellagra? Where nerve cells have died, no amount of therapy will restore them and this should not be blamed on the therapeutic agent. When a specific response takes months to occur, the experiment may be discontinued too soon to detect it. The lesions of pellagra may disappear during a rest in the hospital with no specific treatment. Individual response to exactly similar food depletion varies over a range from slight to severe. In spite of all this, we find that in many reports of researches in human nutrition, controls are often fragmentary or forgotten.

LANCASTER, H. O. AND MADDOX, J. K.: *Diabetic mortality in Australia.* (Med J. Australia, Mar. 11, 1950, 317-322).

Death from diabetes in Australia is exceeded only in the U. S. A. and New Zealand. Probably 30 percent of the Aus-

tralian population carry a diabetic gene. Older females are dying of diabetes at an increasing rate, but male mortality has not changed much. At existing rates of mortality, 1.15 percent of males and 2.89 percent of females are destined to die of diabetes in Australia.

Cereal Food Enrichment in the U. S. A., The National Food Situation (U. S. Dept. Agriculture), July-Sept. 1949, 17-18.

The enrichment of cereal food products with synthetic vitamins and iron has been a significant factor in the increased supplies of niacin, thiamine, riboflavine and iron available for civilian consumption in recent years. The enrichment of all white bread and rolls was required under War Food Order No. 1 from January 1943 till October 24, 1946. About 65 per cent of the white flour sold to civilians as flour, or in products, was enriched during the period of the compulsory program. During 1947 the amount of enrichment of all types exceeded that in 1946 with the exception of the case of high potency riboflavine in the enrichment wafers sold direct to bakeries and restaurants, which showed a slight decline. In 1948, so far as can be determined, there was considerable reduction in all enrichments, although all were increased in the premixes for use in cereal food products other than bread and flour.

PLEYDELL, M. J.: *An outbreak of food-poisoning in Bromyard District.* (Brit. Med. J., July 30, '49, 264-265).

The author describes an outbreak of food poisoning due to infection with *Salm. boris morbificans.* It originated from the eating of beef sandwiches which had been contaminated by infected rodents. The danger of using rat poisons incorporating salmonella organisms, especially in food premises, is emphasized. The female patients were ill about twice as long as the male patients. The evidence suggests that the infection with *S. boris morbificans* does not respond to sulphaguanidine therapy.

TITTLE, G. A.: *Experimental use of methyl testosterone in the premature infant.* (Texas State J. M., Vol. 45, No. 8, 563-564).

Confirming the work of Shelton and Varden, the author found advantages in giving the methyl testosterone orally in 2.5 mg. doses every twelve hours to premature infants of either sex until the body weight had reached 5 pounds. Usually it requires 10 days for the average premature infant to regain its birth weight, but by the use of the hormone this was accomplished in 5½ days. Usually it requires 28 days to reach the 5 lb. level but, by the use of testosterone the time was only 18 days. He also observed equally remarkable improvement in 8 cases of essential malnutrition in premature infants similarly treated. The oral administration of methyl testosterone is said to have no effect whatever on the sex growth of the infant and is safe, and works equally well on either sex. The action in the infant is metabolic stimulation and protein retention.

EDITORIALS

MIDDLE CLASS DIETS IN INDIA

A paper recently printed in the Journal of the Indian Medical Association (May, 1950) by S. Ram, M. A., F. R. I. C., gives the results of a dietary survey of two families of the middle class. Among women, anemia, calcium deficiency and thiamine deficiency are quite common. The middle class male tends to suffer from obesity and not infrequently from hypertension and diabetes. The standards against which comparisons were made are as follows, -2500 cal. for men, 2100 cal. for women and 1100 cal. for children of five or six years of age. The new U. N. average standard is 2600 cal., but people living in India are largely sedentary, shorter in height and not much exposed to cold. The protein standards were, -50 gms. (essential) and 20 gms. (non-essential). Calcium was 0.7 gms. and iron from 15 to 20 mgm. Vitamin A standard was 2000 I. U., thiamine 1500 micrograms and ascorbic acid 50 mg. The dietary survey showed both families deficient in essential proteins and assimilable iron, presumably accounting for the lassitude of the male, and slight anemia in one of the women. The author reconstructs the diets of these two households, increasing the meat and milk allowances so that, at no added cost, more perfect diets could be consumed. Ram's contribution is chiefly important by indicating that in a country where nutrition presents many unsolvable problems, the middle economic bracket at least may be assisted by pure science to procure a practically perfect diet. It would be of great interest if Ram could furnish details of what must or *can* be done to improve the diets of the lowest economic group.

BREAD AS A NUTRITIONAL VEHICLE

The enrichment of bread with thiamine is regarded as perhaps the most effective single nutritional advance yet made. During World War II it was rendered mandatory by Federal law, but the practice still is continued by some baking firms on a voluntary basis. With the growth now of defense activities there is little doubt that enrichment will again become compulsory and will be responsible for giving the nation added physiological impetus. In Newfoundland the bread enrichment program between 1944 and 1948 was credited with having produced definite improvement in the nutritional status of the inhabitants and was reflected in a noticeable reduction in mortality rates. Part of this gain was due to a lifting of import duties on citrus fruit juices.

Provided the cost of bread can be frozen at reasonable levels, it will continue to play a leading role in national nutritional improvement. Enrichment with bone meal or some form of lime salts is indicated by the fact that a large proportion of the population is ordinarily deficient in calcium. Calcium is increased by enrichment with nonfat dry milk, and it has been shown by the University of California that a dry milk increment of from 6 to 14 per cent increases flavor and edibility. Profitable experiments in Syracuse, N. Y., and in New York City suggest that such bread, made with unbleached flour containing 2 per cent wheat germ can be produced at no added cost and is well received.

Enrichment with iron is particularly valuable in war time. During W W II, clinical observers on the home front were impressed by the increased prevalence of iron deficiency anemia among industrial workers in spite of an overall increased *per capita* consumption of meat. Since bread still is the greatest staple of human diet in Western civilization, it may be the recipient of an increasing number of valuable nutrients especially under conditions of national stress.

BOOK REVIEWS

NUTRITION AND DIET THERAPY. Fairfax T. Proudfit and Corinne H. Robinson, 950 pages. The Macmillan Company, New York, 1950. $4.00.

The Tenth Edition of this widely used and popular work presents many changes and additions. The section on normal nutrition had to be entirely re-written because of new knowledge accumulated during the past four years. Vitamins, proteins and amino acids are extensively covered. The section on Diet Therapy is particularly valuable to the physician and medical student. The inclusion of sections on elementary cooking and recipes indicates the scope of the text. The book is one of great value and one marvels how the publishers were able to produce it at the low price quoted.

RECENT ADVANCES IN CHEMOTHERAPY. VOLUME I (3RD EDITION). G. M. Findlay, 625 pages. The Blakiston Co., Philadelphia, 1950, $7.50.

Volume I of this extremely detailed work covers the history of chemotherapy and deals with its application in diseases due to insects, helminthic infections, amebiasis, babesias and other protozoal infections, leishmaniasis and trypanosomiasis. Volume II will be devoted to malaria, volume III to bacterial, rickettsial and virus infections, volume IV to a survey of sulphonamides and antibiotics. The book, which completely fulfills the needs of the physician and veterinarian, is written in a charming style and is heartily recommended.

GENERAL ABSTRACTS

GESSLER, ALBERT E., GREY, CLIFFORD E., SCHUSTER, MARY C., KELCH, JOHN J., AND RICHTER, MAURICE N.: *Notes on the electron microscopy of tissue sections. 1. Normal tissue. 2. Neoplastic tissue.* Cancer Research 8, 11, 534-573, November 1949.

Methods of sectioning, for the electron microscope, by the high speed microtome to the thickness of the order of 1/10 of 1 micron have been developed, as well as auxiliary techniques of fixing and embedding of specimens, to produce electron micrographs possessing satisfactory detail with a minimum of distortion by coagulation and shrinkage. These methods have been employed for the investigation by the electron microscope of sections of normal animal and human tissue. Greater detail in general and some observations in particular have been presented by this method which are not revealed by the light microscope, since dimensions are often involved which are below the instrument's threshold of resolution. Consistently, the outer and nuclear membranes in the normal appear as firm and well-defined boundaries. The nuclei are generally well formed with fine granular texture and much denser nucleoli. The cytoplasm seems to be characterized by a coarser background with well-defined and denser granular particles while the intercellular tissue shows a submicroscopic fibrillar structure.

In neoplastic tissue sections, however, signs of aberration were observed. They seem to begin with the appearance of large numbers of vacuoles in intercellular tissue and cells. A characteristic aberration seems to be the breaking or disappearing of nuclear membranes and subsequent shrinking or breaking of the nuclear mass into dense fragments. A similar breaking of the outer cellular membranes frequently goes hand in hand, accompanied by the appearance of fibrils replacing them and often filling the cell interior. Every precaution has been taken to use only portions of tumors believed to be viable. The authors believe that some of the phenomena are signs of neoplasia.

Franz J. Lust.

HODES, PHILIP J. AND MAMMOSER, LAMBERT: *Amebiasis.* Am. J. Roentg. & Radium Th. 57, 3, 329, March 1947.

The authors studied 92 cases, of which 60 who passed cysts were asymptomatic. Nothing noteworthy was found in the esophagus and stomach. The passage through the small intestines was rapid. The small intestinal pattern was normal including the terminal ileum. Considerable difference seemed to exist between the appearance of a cecum demonstrated by the oral meal and the cecum when outlined by barium enema. Not infrequently the oral meal revealed an irritable, non-retentive cecum which looked normal by barium enema. This suggested that the oral meal was a more sensitive and more reliable indication of an irritable cecum in early amebic typhlitis. By barium enema, minor abnormalities were noted, irritability of different parts of the colon were detected, however, irritability and tenderness were not always localized in the same portion of the colon.

Franz J. Lust.

GOTTLIEB, MOGENS CHRISTIAN: *Multiple chylus cysts.* (Nordisk Medisin, 43:178, 1950).

A woman, 52 years old, had suffered from steatorrhea during ten years. The difficulties in making a correct diagnosis of the primary cause in cases of steatorrhea are mentioned. The diagnosis in this case of multiple chylus cysts was obtained by autopsy.

O. W. Huschye, Oslo.

TANTURI, C. A., LONCHARDI, J. A. AND BARFI, R. F.: *Protective action of sulfanilamide on experimental chloroform hepatitis.* (Surg. Gynecol. Obstet., v. 84, p. 477, 1947).

For a period of five days prior to anesthesia with chloroform dogs were given daily doses of 150 miligrams sulfanilamide per kilogram body weight. Anesthesia with chloroform for one hour was the hepatoxic agent. Usually such anesthesia results in a certain amount of liver damage. In the sulfanilamide pretreated animals the incidence and severity of hepatitis was less. Administration of the sulfonamide during anesthesia was ineffective in protecting against liver damage.

POPPER, H. L. AND NECHELES, H.: *Transition of pancreatic edema into pancreatic necrosis.* (Proceed. Central Soc. Clin. Res., v. 20, p. 65, Nov., 1947).

In the presence of edema of the pancreas the temporary clamping of the upper pancreatic artery results in the progression of the edema to necrosis. The authors believe that spasm of the arteries plays a role in the development of pancreatitis.

ISAAC, F., OTTOMAN, R. E. AND WEINBERG, J. A.: *Roentgen studies of the upper gastrointestinal tract in vagotomy.* Am. J. Roentgen. & Rad. Therapy 63:1, 66-74.

In a careful study of 83 cases of vagus section, the stomach showed decreased peristalsis, delayed motility, loss of tone and dilatation. These defects in function disappear only very gradually so that, after six months, nearly half the cases still show decreased peristalsis and delayed motility. A majority of the cases having demonstrable ulcer crater in the duodenal bulb before operation showed a disappearance of the niche after vagotomy. In the small gut the most constant changes consist of dilatation of the duodenum and delay in intestinal motility.

TEITELBAUM, M. D. AND ARENSON, N.: *Recurrent small intestinal intussusception in children.* Am. J. Roentgen. & Rad. Therapy, 63:1, 80-88.

The authors found small intestinal intussusception in young children more frequently than is commonly believed. It is presumably a manifestation of neuromuscular dysfunction and, in some cases, it may be an allergic response. The intussusception, which is transient, recurrent, usually involving multiple segments of the small gut, produces rather con-

stantly intermittent abdominal pain with nausea and sometimes vomiting. The symptoms may be present for months and years and the single attacks may be severe. However, there is no strangulation or obstruction. No tumor masses can be felt and there is no bleeding from the bowel.

Arnott, D. W. H.: *Psychiatric aspects of dyspepsia in soldiers.* (Med. J. Australia, 37, 1, 5, 143-145).

Eight and five-tenths per cent of patients referrred for psychiatric consultation had dyspeptic symptoms — nausea, vomiting, anorexia, weight loss, belching, sinking feelings in the stomach, intestinal hurry, sour stomach, heartburn, as well as other digestive symptoms difficult to describe. All were suffering from anxiety hysteria, and had been disorganized by stress. Unresolved emotional tension had merely "spilled forth through the gastric and intestinal systems." Cure required usually discharge from the army. The author remembers a "long line of frustrated, weeping, desperate or broken men, for whom army life had proved too heavy a burden."

Cantor, M. O.: *Radiological criteria for removal of intestinal decompression tube.* (Radiology, 54, 4, 535-540).

Cases are presented to indicate the value of the Cantor tube in intestinal obstruction. It is also shown that x-ray studies following the injection of barium suspension is an accurate method of determining the persistence of actual obstruction, and whether surgery is or is not required.

Schwartz, S. O.: *Severe anemia secondary to diaphragmatic hiatus hernia.* (Illinois Med. J., 97, 4, 204-210).

Bleeding from the stomach in hiatus hernia may produce profound iron-deficiency anemia and usually there are few symptoms to direct the attention to the G.I. tract. In persons past middle life without a history of overt bleeding, without localizing symptoms and without significant physical findings, the lesion should be searched for at once, before considering any other diagnosis.

Armestar, A. M.: *Contribution to homologous serum hepatitis.* (Arch. Peruanos de Patol. y. Clin., Dec. 1948, Vol. 11, No. 4, 537-552).

The author reports on 10 cases of homologous serum hepatitis. It is rare in Peru, but does occur. It occurred in five per cent of all transfusions done. These patients reacted favorably in five or six weeks, but death occasionally occurred, the mortality rate being 0.24 per cent of the transfusion practice. No case was observed in children, all occurring between 29 and 59 years of age. It usually began without fever, but when fever was present it was around 38 degrees centigrade. In spite of the fact that foreign authors emphasize that hepatitis is more frequent when plasma is utilized, his cases resulted from the use of whole blood, except for two cases in which plasma was used. There should be a better control over the donors in order to discard those in which there has been any suspicion of the existence of hepatitis or those who had recently had an attack of jaundice.

Ocampo, L., Mora, C. M. and Vela, J.: *Anomalies of the gallbladder and biliary passages in emergency surgery.* (Arch. Peruanos de Patol. y. Clin., Dec. 1948, Vol. 11, No. 4, 576-578).

A case is presented of congenital absence of the gallbladder with a coexisting cavernous hemangioma. They emphasize in these cases that one often sees a picture of an acute abdomen with hepatic colic of the gallbladder type, particularly those with intra-hepatic lithiasis. Cholangiography at the operating table is very important in diagnosing these cases.

Borch-Madsen, Povl: *Foreign bodies in the gastro-intestinal tract.* Nordisk Medisin, 1950, 43:176.

An account is given of some cases of perforation of the stomach by foreign bodies, in one case to the abdominal wall and in three cases to the peritoneal cavity. The treatment is especially discussed.

O. W. Huseby, Oslo.

Strang, Christopher: *Factors associated with perforation in peptic ulcer.* Br. Med. J. No. 4658, p. 873, April 15, 1950.

The author reports 189 cases. The great preponderance of males and the high incidence of duodenal ulcers was confirmed. In men, perforated duodenal ulcer was four times as common as perforated gastric ulcer. In women, however, perforated gastric ulcer was twice as common as perforated duodenal ulcer. In 91 per cent of patients a history of previous indigestion was obtained; in 64 per cent this conformed to a typical ulcer pattern. In 68 per cent the history of indigestion lasted for longer than one year. The onset of perforation seemed to be unrelated to individual habits of eating, drinking, or smoking, or to a particular phase of digestion, and the moment of perforation was not correlated with the position of the patient, straining or physical activity. Perforation occurred less often in the autumn than in the other seasons! The daily incidence varied little, but perforation was more frequent from midday to midnight than in the morning hours.

In the three days preceding perforation, 22 per cent had constant abdominal pain, 37 per cent intermittent pain, 28 per cent no pain (?!), and 13 per cent such vague symptoms as heartburn or nausea. There was no specific pattern of symptoms which led up to a perforation, this seemed to be an unpredictable complication.

Franz J. Lust.

Moutier, Francois and Nemours-Auguste: *The subcardial and juxta esophageal cancer of the greater curvature of the stomach.* Arch. L'Appareil Digestif 37, 3-4, 137-164, March-April 1948.

This is an excellent article of the diagnosis of the cancer of the cardiac region of the stomach. The roentgenological diagnosis of tumors of this region is described and the emphasis is put on the visualization of malignancies. The authors show the importance of the positioning of the patient and of the air bubble into which the tumor protrudes. Excellent roentgenograms and drawings of the findings illustrate the paper. Dysphagia has not been present, neither clinical nor roentgenological, in these tumors, just as a stenosis of the cardia only develops, when the condition has progressed. In a further communication on pages 201-207 of the same journal, the authors discuss the roentgenological study of the left lobe of the liver, which might give similar signs of a tumor protruding into the magenblase.

Franz J. Lust.

Parnes, Irving, H.: *Nonparasitic cysts of the spleen.* J. Mt. Sinai Hosp. New York 16, 4, 245, Nov.-Dec. 1949.

Two cases of cyst of the spleen are reported: one epidermoid in character, the other a false cyst of traumatic origin. Both were in young women. One patient had completed a normal pregnancy 18 months before onset of symptoms, which were ushered in by acute abdominal pain, most probably due to a partial rupture of the spleen. The other patient had had infectious mononucleosis seven months before onset of the recent symptoms which consisted of dull and sharp pains in the left upper abdomen. Splenectomy was performed in both cases. The roentgenograms and the photos of the specimens are reproduced.

Franz J. Lust.

Dragsted, J. P.: *The Guillain-Barré-Neel syndrome as a complication of acute hepatitis.* Nordisk Medisin, 1950, 43:600.

A case is presented of typical polyradiculitis of the Guillain-Barré type, developing in a 12 year old boy a few days after he had recovered from acute viral hepatitis. Since the syndrome was described by the Danish neurologist, A. Neel, concurrently with, but independently of, Guillain and Barré, it is proposed that it be called the Guillain-Barré-Neel syndrome. An interesting feature of the present case is that the patient had suffered from a similar syndrome ten years earlier, but had recovered as rapidly as he did after the second attack.

O. W. Huseblye, Oslo.

Demole, M.: *Dents et dyspepsie. Teeth and digestive diseases.* (Rev. Med. Suisse romande, 25 March, 1929, 69, No. 3, 177-191).

If we admit what statistics seem to prove, then patients who suffer from digestive diseases possess a worse set of teeth (42 per cent instead of 30 per cent) than those without. D. studies first the influence of dyspepsia on the teeth:

nutrition trouble due to chronic gastro-intestinal diseases; the part of gastric acidity in the salivary pH; the importance of the gum as an organ for excretion; the abatement in the work of chewing owing to bland "smooth" diet.

How the condition of the teeth influences the digestive organs is easier to imagine and to demonstrate. It can be a state of infection occasioned by swallowing putrid or toxic substances from the teeth; or a focal infection starting from a granuloma or from the gums (proved by culture of blood, collected in the gum).

On the other hand, a defective chewing (*dysmastasia*, Demole), as it happens in toothless patients, in those who eat too quickly, etc. . . . occasions disorders of mechanical origin: the food is not made into small enough pieces, or by a reflex, with a repercussion on the salivary and gastric secretions.

M. Demole (Geneva).

MILHAUD, G., PFISTER, C. ET LE COULTRE J.: *Le gel au Formol. Ses fondements physico-chimiques et son importance en clinique* (*The formaline-gel reaction; its physico-chemical basis and its clinical value*) (Helv. Med. Acta, May 1949, vol. 16, No. 2, 110-137).

After recalling the methods used to make a desiquilibrium of the protides in the blood conspicuous, the authors write the history of the formaline-reaction, and try to elucidate its mechanism. The reaction itself consists in adding two drops of neutral formaline at 35 per cent to 1 cm³ of serum. The gel appears between 24 and 48 hours; after that time, the reaction can be considered as negative. An acid formaline is more active, and a temperature of 40° C gives the quickest reaction.

When using Cohn's method in separating plasma, the authors are able to ascertain that the α-globuline reacts very slowly, that the albumins do not invite any freezing process and that the protein fractions responsible for a positive reaction are the fibrinogen and the γ-globulins. The fibrinogen gelifies, when concentrated four times less than the mixture of globulins β and γ. Albumins have practically no inhibitive influence on the reaction, and consequently a hypoalbuminemia is not sufficient to make the serum positive. The electrophoretic analysis confirms that α-gel process generally indicates an increase in the rate of the γ-globulin in the serum. The accumulation of fibrinogen creates plasmas gelifying much more rapidly than the corresponding serum. A positive reaction has been proved 120 times during 1,958 routine examinations. Positive cases showed specially cirrhosis, hepatitis, chronic alcoholism, pulmonary tuberculosis, syphilis, chronic rheumatism.

M. Demole (Geneva).

LUSHBAUGH, CLARENCE C.: *Infiltrating Adenomatous Lesions of the Stomach, Cecum and Rectum of Monkeys Similar to Early Human Carcinoma and Carcinoma in Situ*, Cancer Research, July 1949, Vol. 9, No. 7, pg. 385-394.

The experimental production in animals of neoplastic gastro-intestinal lesions of types common in man has proven extremely difficult and, in the case of most lesions, rarely successful. Only recently has experimental carcinogenesis in the intestine of rodents been successful with sufficient constancy to be of aid in the study of the pathogenesis of cancer. Therefore the repeated production of carcinoma-like lesions in the stomach, colon and rectum of monkeys who had ingested motor lubricating oil is of great interest.

Thirty-six rhesus monkeys were used in these experiments. Three experiments were performed. In the first, 22 monkeys used by other investigators for various purposes were necropsied and the gastro-intestinal tracts investigated for disease. The second experiment comprised an attempt to reproduce the lesions originally found in monkeys exposed to aerosols of oil. Ten ml. of oil were sprayed onto the chest and abdomen of five monkeys daily until the animals became moribund, a period ranging from 100 to 213 days. Five other monkeys served as untreated controls and were killed simultaneously with the moribund treated monkeys. In the third experiment, four monkeys were used. Instead of the usual diet of dog chow and cabbage, these monkeys received synthetic diets, containing no proteins, in order to determine whether protein inanition, which accompanies intoxication with the oil, could alone produce the hyperplastic infiltrative gastro-intestinal lesions observed after treatment with oil.

To the author these experiments have demonstrated that infiltrating adenomatous lesions of the rhesus monkey can be produced with a high percentage of success by feeding the animals this type of motor lubricating oil. Two instances where the gastric sub-mucosa was invaded by cystic mucosal glands in monkeys who were not in contact with the oil seem to indicate that this oil is not the only agent producing these changes. Evidently the gastric and colonic mucosae of the rhesus monkey are extremely reactive to non-specific irritative substances. Protein starvation alone did not produce these reactive changes. The microscopic similarity of the many instances of atrophic and hyperplastic gastritis to these conditions in man appear to indicate that the mucosa of the monkey reacts similarly to that of the human stomach and colon.

By the usual histological criteria, many of these lesions would be called cancerous. Experimentally, however, they cannot be classified as malignant neoplasia. Inflammation and infection appear to play as great a role in the production of these lesions as does the oil.

Walter Cane.

JOHN, H. J.: *Dietary invalidism.* (Ann. Int. Med., 32, 4, 595-610).

John describes many conditions in which malnutrition may develop to a point of serious invalidism. Among these he includes obesity where excess calorie intake is responsible, but most instances are found where the patient's diet has been erroneously and too rigidly restricted in calories. The mistaken diagnosis of diabetes, as in renal glycosuria and hyperthyroidism, is often responsible for needlessly severe restriction of carbohydrates, but it should be borne in mind that 2.3 per cent of hyperthyroid cases eventually become true diabetics. Dietary deficiencies may be due to geographic conditions (e.g., the over-use of corn grits and sow belly in the South), alcoholism, dietary idiosyncrasies or starvation erroneously prescribed in food allergies. He refers to the dietary insufficiency of ulcer diets, especially as formerly prescribed, and states that in the past 50 years at least 46 different types of diet and 108 different drugs, vitamins, sex hormones etc., have been used in ulcer therapy.

PALMER, W. L., KIRSNER, J. B. AND MARSHALL, H.: *Therapeutic considerations in chronic ulcerative colitis.* (Ann. Int. Med., 32, 4, 627-639).

The authors believe chronic ulcerative colitis is a true inflammatory disease in which infection of some sort plays a considerable role, and that emotional factors, if not primary, are of great importance in the course and treatment. Points of therapeutic importance are rest; a high-calorie, high-protein, low residue diet; blood transfusions; belladonna, sedatives, chemotherapeutic drugs, antibiotics, psychotherapy and surgery. Sometimes "medical ileostomy" (Miller-Abbott Tube) is of value. Surgery is of chief value for complications. In some cases psychoanalysis appears to produce definite and permanent changes in the personality, particularly in young persons.

LADIN, PHILIP: *The Delayed Treatment of Appendiceal Abscess.* New York State Journal of Medicine, Vol. 50, No. 6, 1950, Pg. 681-685.

The delayed treatment of peritonitis of appendiceal origin dates back to 1901 when Ochsner first described it. At that time he reported striking improvement over the usual results of his day. There have been scattered reports since then of successful treatment by this method. Recent experimental work has shown that high concentrations of penicillin in the blood and serous cavities inhibit the growth of B. coli. It has also been shown that the concentration in ascitic fluids and blood is directly proportional to the dosage of penicillin given intramuscularly and intravenously. The theory was postulated that B. coli inactivates penicillin and therefore massive doses are necessary to overcome this inhibitory effect. It seemed logical that combining Ochsner's method with present day supportive treatment and antibiotics should give the best results. The peritoneum is well able to handle the infection if not interfered with, and these patients can then be operated upon at a future date with minimal risk. Three of the patients reported showed an appendix divided into two halves with the ends sealed off and no evidence of leakage. The author points out that the readiness with which these patients return for further surgery has been noted by others as well as by him. Four to six weeks appears to be a safe time for the secondary operation under this regime of

treatment and primary union can be obtained in these patients. The only disadvantage to this form of treatment is that it requires careful and frequent observation, and the exercise of good clinical judgment as to when, as well as whether or not, to intervene. Six cases of appendiceal abscess treated by this method are reported in detail. The patients vary in age from two to 46, and presented a variety of clinical pictures. The temptation to interfere surgically is probably so great that it is a major factor in the failure of this method of treatment to become more popular in spite of repeated reports as to its superiority.

Franz J. Lust.

SIRIS, IRWIN E.: *Malignant tumors of the small intestine.* Am. J. Surg. 77, 5, 573, May 1949.

Four cases of malignant tumors of the small intestine have been presented. The underlying morbid process was different in each case. They illustrate the difficulty in early recognition and the reasons for the grave prognosis. (1) The early symptoms are vague intermittent abdominal distress and distention bearing no relation to meals; followed by progressive weakness and severe anemia. (2) Radiographically, the disease is variously diagnosed and a correct interpretation is rarely made before the onset of partial obstruction. (3) With the onset of obstruction, the disease is generally too far advanced to achieve a successful outcome. (4) The disease frequently extends to the mesentery, which is foreshortened. The lymphatic spread precludes radical extirpation of the inaccessible lymphatics. (5) Metastasis and early recurrence within a few weeks to two years is to be expected if thorough extirpation of involved lymphatics cannot be effected. The disease is resistant to radiotherapy.

Extirpation of malignant tumors of the small intestine, even in advanced stages is attended with a relatively low immediate operative mortality, therefore, earlier recognition of the disease may enhance the ultimate result. This may possibly be accomplished by 1) close evaluation of the history, 2) improvement in radiographic studies in order to ferret out the early intra- or extraluminary encroachments and 3) comprehensive repeated laboratory investigations particularly for occult blood in the stools.

Franz J. Lust.

RISFELT, O.: *Mortality and prognosis in acute pancreatitis.* Nordisk Medisin, 1950, 43:573.

A study of the literature shows that the relatively high mortality in surgical treatment of acute pancreatitis has been largely due to shock. By intensive treatment of the shock it should be possible to reduce the mortality considerably. In cases where the diagnosis may be doubtful, exploratory laparotomy should be done in order to exclude peritonitis due to other causes. This procedure will not lessen the patients' prospects of recovery.

O. W. Huseby, Oslo.

RISFELT, OVE: *Diagnosis of acute pancreatitis in the absence of diastasuria.* Nordisk Medisin, 1950, 43:577.

Thirteen cases of pancreatitis, 11 of which were verified by operation or autopsy, are reported. Six cases did not show elevated diastase values, although the first examination took place within 48 hours of the onset of the disease. In eight patients, exploratory laparotomy was necessary owing to the severe abdominal symptoms. Two of these patients died. Three of the non-operated patients died, two of them of pulmonary embolus. The importance of the shock condition for the prognosis is discussed.

O. W. Huseby, Oslo.

"WHAT PATIENTS READ"

New Schering News Letter for Doctors

"Medicine in the News," which is also known as *"What Patients Read,"* is the title of a unique new monthly publication now being mailed as a service to physicians by Schering Corporation, pharmaceutical manufacturers of Bloomfield, New Jersey.

Many articles on medical and scientific subjects are currently appearing in lay magazines, newspapers and books. Editors have found that the public is interested in such articles. Some of these news stories merely review in elementary fashion what is known about diagnosis and treatment in a given field. Others describe new developments not yet revealed in published research articles in the scientific and medical literature. These create for the practicing physician serious problems in patient relationships and therapy.

Schering now summarizes many of the popular scientific stories each month and presents them in a concise news-letter form which may be quickly read. This news bulletin constitutes a report to physicians on the medical topics discussed in the lay press. No editorial comments are made. Physicians can now easily find out ahead of time what their patients will read or have been reading in the lay press.

The release of *"Medicine in the News"* by Schering was no chance development. As more and more medical research discoveries are brought by science writers to the attention of an increasingly interested public, the need for such a service became apparent to Schering's executives. Physicians themselves asked for it, and several medical journals printed editorials and articles citing the need. An extensive coast to coast program of opinion-testing was carried on among physicians before Schering finally put the project into regular publication. The demand which resulted was overwhelming, however, and the bulletin has been hailed by physicians as a novel approach in answer to one of their problems.

NOTICE

At the meeting of the Board of Internal Medicine in San Francisco, Dr. Hugh R. Butt, Mayo Clinic, Rochester, Minn., was elected to membership on the sub-specialty board in gastroenterology as a representative of the American Gastroenterological Association. This election will be for a term of five years expiring July 1, 1955. Dr. Lowell D. Snorf, Evanston, Ill., was elected a member of the sub-specialty board to represent the section on gastroenterology and proctology of the American Medical Association. This election is for a term of four years expiring July 1, 1954.

CHLORESIUM POWDER

Description: A therapeutic chlorophyll preparation for the treatment of peptic ulcers.

Composition: Water-soluble derivatives of chlorophyll plus the antacids, aluminum hydroxide and magnesium trisilicate in a base of dehydrated powdered okra. Each individual packet (1 dose) contains 1.8 gm. of powder.

Advantages: Chloresium Powder is specifically designed to bring to the treatment of peptic ulcers the tissue-stimulating properties of water-soluble chlorophyll. The specially prepared okra base provides a tenacious coating material which performs the essential function of holding the chlorophyll in prolonged contact with the ulcer crater. The addition of aluminum hydroxide and magnesium trisilicate provides prompt antacid action without danger of alkalosis or interference with bowel regularity.

In clinical trials Chloresium Powder proved particularly effective in chronic ulcer cases which had resisted previous therapy; an unusual aspect of these trials was that the successful results were obtained without benefit of restrictions on diet, smoking, alcoholic beverages or general activity.

Dosage: The average dosage is 5 powders (individual packets) daily — one upon arising, one upon retiring, and one after each meal (1½ hours after meal). Powder is placed on tongue and swallowed with the aid of a small amount of water. Fluids or solids taken within one and one-half hours after taking powder lessen effect of powder and should be avoided whenever practicable.

Packaging: Chloresium Powder is packaged in an attractive light green slip-label carton containing 25 individual glassine packets. The suggested retail price is $2.00 per carton.

MUMPS CAN BE PREVENTED

Developers of many biological products now universally used, Lederle Laboratories again pioneer in the immunization field with the introduction of a vaccine for the prevention of mumps.

MUMPS VACCINE *Lederle* is designed primarily for the immunization of large groups of children or adults, housed together in close quarters, as in schools, camps, institutions, or military installations, where a mass outbreak of mumps would cause serious inconvenience. It is, therefore, not recommended for routine use in the prevention of mumps in childhood, inasmuch as it confers immunity for only about one year and annual revaccination is necessary.

It is estimated that approximately 80% of urban residents contract mumps before the age of 17 when it ordinarily causes few complications. However, mumps can cause inflammation of the reproductive glands, possibly leading to sterility, and may even develop as a type of meningitis. In adult life, therefore, it is a serious disease. For this reason it may be advisable to administer MUMPS VACCINE Lederle to susceptible doctors, nurses, college students, military personnel, etc.

MUMPS VACCINE Lederle, prepared from chick embryos, was developed primarily by Dr. Victor Cabasso of the Viral and Rickettsial Disease Research Section under the direction of Herald R. Cox at Lederle Laboratories, following the adaptation of the virus to the chick embryo by Dr. Karl Habel, of the National Institute of Health, and Dr. John F. Enders, of the Children's Hospital, Boston, Massachusetts. The vaccine is packaged in vials of 2 cc. and 10 cc., representing one and five immunization doses.

WINTHROP-STEARNS INC. ELECTS NEW VICE PRESIDENT

Sidney C. Mills has been elected vice president of Winthrop-Stearns Inc., assigned to administrative operations. Dr. Theodore G.

Spasmolysis plus!

For the patient presenting a clinical picture in the knot of spasm and spastic pain, Donnatal provides controlled spasmolysis, through a precise optimal balance of the principal *natural* alkaloids of belladonna

plus central and peripheral sedation *plus* freedom from toxic reaction *plus* choice of alternate dosage forms *plus* broad therapeutic applicability in spasm of the gastro-intestinal, biliary, urogenital, respiratory and central nervous systems *plus* outstanding economy

Each tablet or capsule, and each 5 cc. of elixir contains:

Hyoscyamine Sulfate	0.1037 mg.
Atropine Sulfate	0.0194 mg.
Hyoscine Hydrobromide	0.0065 mg.
Phenobarbital (¼ gr.)	16.2 mg.

A. H. Robins Co., Inc. • Richmond 20, Virginia

Robins — Ethical Pharmaceuticals of Merit since 1878

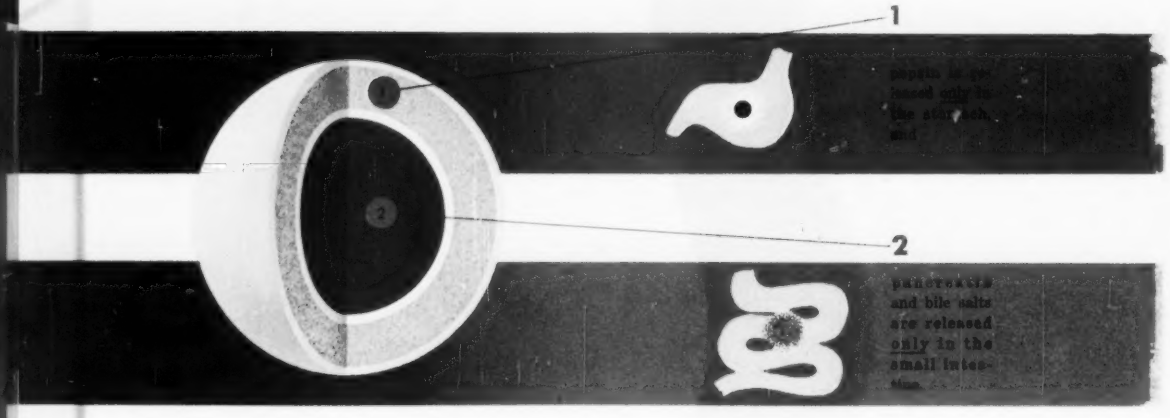
donnatal®

elixir, tablets, capsules

for effective relief of visceral spasm . . . Donnatal Elixir acceptable to all ages as spasmolytic alone, or as a therapeutic vehicle for adjuvant medication.

now... digestant enzymes released in relay by the peptomatic* tablet

*A coined word to describe the unique mechanical action of the Entozyme Tablet, whereby:



The multiform aid required in digestional dysfunction or imbalance may now be administered in a single tablet—Robins' Entozyme—which (by unique Peptomatic* action) releases pepsin, pancreatin and bile salts individually at the gastroenteric levels of respective optimal activity. Entozyme has proven particularly efficacious[1,2] in chronic cholecystitis, post-cholecystectomy syndrome, infectious hepatitis, pancreatitis, chronic dyspepsia, and peptic ulcer. It is also especially useful in nausea, anorexia, belching, flatulence and pyrosis.

formula:

Each specially constructed tablet contains pancreatin, U.S.P., 300 mg.; pepsin, N.F., 250 mg.; bile salts, 150 mg.

references

1. McGavack, T.H., and Klotz, S.D.: Bull. Flower Fifth Ave. Hosp., 9:61, 1946. 2. Weissberg, J., et al.: Am. J. Digest Dis., 15:332, 1948.

Robins **entozyme®**

The multi-enzyme digestant with unique Peptomatic Action!

A. H. Robins Co., Inc. · Richmond 20, Virginia

Ethical Pharmaceuticals of Merit since 1878

Klumpp, president, announced recently. He has been administrative assistant to the president and assistant treasurer of the Company for the last four years. Mr. Mills will be located at Winthrop's new offices at 1450 Broadway.

Joining Winthrop in 1936, Mr. Mills has served as New York manager of the retail sales division; regional manager for the midwest; manager of the Atlanta and Chicago divisions; assistant division manager of the St. Louis division, and salesman in the southwest territory. Mr. Mills has been in the drug business, both in retailing and manufacturing since 1923.

Born in Whitesboro, Texas, October 20, 1903, Mr. Mills attended schools in Chickasha, Okla., receiving his Ph.G. degree in 1923 from the School of Pharmacy, University of Oklahoma. He is a member of the American Pharmaceutical Association.

Mr. Mills lives at Manhasset, L. I., with his wife, the former Evelyn Turriff of Tulsa, Okla., and their two sons, Sidney, Jr., and Don.

CHLOR-TRIMETON MALEATE SYRUP

Manufacturer: Schering Corporation, Bloomfield, New Jersey.

Active Constituent: Chlorprophenpyridamine maleate (1 - parachlorophenyl - 1 - (2-pyridyl)-3 - dimethylaminopropane maleate).

Action: Inhibition of histamine effects produced by allergens. Markedly increased pharmacologic activity over all other available antihistamines.

Indications: Adjunctive therapy in all allergic conditions responding to antihistaminic therapy, such as hay fever, vasomotor rhinitis, urticaria, gastrointestinal allergies, drug reactions and other allergic manifestations. Because of its high potency, it is indicated in many out of the ordinary cases such as tuberculous reactions, transfusion and serum reactions, insect bites, measles, chicken pox and other exanthematous eruptions which respond with the same lack of side actions.

Dosage: Adults and adolescents: 1 to 2 teaspoonfuls 3 to 4 times daily.

Children: ½ to 1 teaspoonful 3 to 4 times a day, depending on age and size of the child.

Packaging: Chlor-Trimeton Maleate Syrup each teaspoonful (4 cc.) containing 2 mg. of Chlor-Trimeton Maleate: bottles of 15 ounces.

SCHERING APPOINTS NEW SALES SUPERVISORS

Mr. Arthur M. Schmidt, formerly Mid-Atlantic District Supervisor of Schering Corporation's Eastern Division, has been appointed Eastern Division Supervisor, according to an announcement by Dr. John N. McDonnell, vice-president of that pharmaceutical manufacturing organization of Bloomfield, New Jersey.

Mr. Schmidt is a graduate of Philadelphia College of Pharmacy and Science. In addition to hospital administrative work and retail pharmacy practice, he has had extensive sales and supervisory experience with Schering and with previous affiliations.

Also announced was the appointment of Mr. J. Roger Cox as Mid-Atlantic District Supervisor, succeeding Mr. Schmidt. After his graduation from the Philadelphia College of Pharmacy and Science in 1936, Mr. Cox was in retail pharmaceutical practice for a number of years, and served for four years in the U. S. Army. He joined Schering in 1946 as a Professional Service Representative.

UPJOHN MAKES AVAILABLE TWO ADRENAL CORTEX HORMONES FOR CLINICAL TESTING

The Research Division of The Upjohn Company, Kalamazoo, Michigan, one of the oldest producers of adrenal cortical hormones, has succeeded in preparing two active adrenal steroids. These two compounds, corticosterone, known as compound B, and 17-hydroxycorticosterone, compound F, have been supplied recently for limited clinical testing in rheumatoid arthritis and Addison's disease. However, it is to be emphasized that the amounts available do not allow further distribution of these substances at the present time.

Both of these compounds differ from cortisone, best known of the adreno-cortical hormones, in having a hydroxyl group rather than a ketone group at the 11-position on the steroid nucleus. In addition, corticosterone lacks a hydroxyl group at the 17-position.

The introduction of the hydroxyl group at the 11-point position has been considered a major chemical hurdle, and its accomplishment by the Upjohn group represents an important contribution to adrenal hormone research.

SCHERING'S FAR EASTERN SUPERVISOR VISITS HOME OFFICE

Mr. Leonard Chan, Supervisor for China and Hongkong operations of Schering Corporation, pharmaceutical manufacturers of Bloomfield, New Jersey, recently visited the home offices for consultation with Mr. Jay R. Hunt, Schering's International Division Manager, on marketing problems in the Far East. The development and promotion of new Schering products in China and Hongkong and their impact on those markets was discussed, as well as exchange and import problems associated with the relatively unstable market areas in the Orient.

Mr. Chan, a pharmacist and a graduate of the University of California, has been associated with Schering Corporation since 1946.

PENICILLIN TABLETS IN NEW BULK PACKINGS

New York, N. Y.—(Special)—Winthrop-Stearns Inc., is introducing new bulk packings of Penicillin Potassium G Buffered Tablets and Penicillin Potassium G Soluble Tablets.

Both products previously available in bottles of 12's now come in 50,000 and 100,000 units in 100's. The Penicillin Buffered Tablets are also packed in 500's.

Commercial introduction of the new packings was effective July 10.

WINTHROP-STEARNS MODIFIES PROCAINE PENICILLIN FORMULA

A modification of the formula for Procaine Penicillin for Aqueous Injection is announced by Winthrop-Stearns Inc. Added to the previous formula is a 1 per cent Sodium Citrate content, which acts as a buffering agent. The company states the resulting product is "more stable and more easily suspended."

rational therapy

through Specific Action in Diarrhea and Infectious Enteritis

Paoguan presents sulfaguanidine, colloidal kaolin, and pectin for prompt action in many forms of infectious diarrhea, colitis, and gastroenteritis. Produces rapid relief of the diarrhea and associated abdominal discomfort.

Antibacterial The antibacterial action of sulfaguanidine is largely confined to the intestinal tract. It is but slightly absorbed, hence is remarkably free of toxic systemic reactions. It is the sulfonamide of choice in many forms of infectious enteritis.

Demulcent Pectin performs the valuable function of combining with certain toxins and exerting a well-defined demulcent influence upon inflamed intestinal mucous membranes.

Adsorbent Both kaolin and pectin are highly adsorptive and aid in the removal of toxins and bacteria, reducing the severity of the invasion.

Paoguan is available through all pharmacies in gallon and pint bottles.

THE S. E. MASSENGILL COMPANY
Bristol, Tenn.-Va.
NEW YORK • SAN FRANCISCO • KANSAS CITY

SEM CO

Each 5 cc. of Paoguan contains:

Sulfaguanidine	0.5 Gm.
Colloidal kaolin	2 Gm.
Pectin	0.04 Gm.

Combined in a palatable vehicle containing aromatics and carminatives.

PAOGUAN

SULFAGUANIDINE • PECTIN • KAOLIN

Effective alone . . . better together

Dehydrocholic Acid:
for a flushing effect upon the bile passages.

NOTE THE NAME

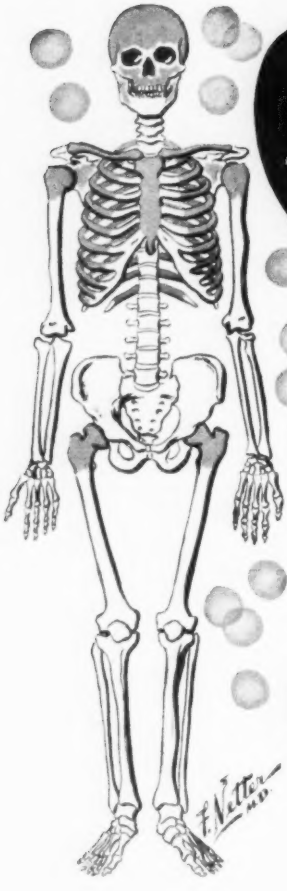
Hydro-◯-Bilein®

(BILEIN® AND DEHYDROCHOLIC ACID, ABBOTT)

Bilein:
for an effective concentration of bile salts.

Sometimes you want the choleretic action of natural bile salts, sometimes the hydrocholeretic action of oxidized bile salts—usually you want both. Now you can prescribe both in one easy-to-take preparation, HYDRO-BILEIN.

Each HYDRO-BILEIN tablet contains 2 grs. dehydrocholic acid and 2 grs. dried, purified ox bile. Administered simultaneously, the maximum effect is obtained from each—the one sluicing out inspissated bile or products of inflammation from the biliary tract, the other stimulating the production of bile solids. Together they facilitate gall bladder emptying and increase intestinal motility. The average dose is one tablet two to four times daily, preferably after meals. Dosage may be reduced if it produces an undesired laxative effect. Your pharmacy has HYDRO-BILEIN in bottles of 100 and 1000 sugar-coated tablets. Abbott



Shaded areas indicate zones of active red bone marrow in the adult human.

"MARROW-CONSCIOUS" THERAPY IN SECONDARY ANEMIA

In the adult, actively hemopoietic red bone marrow is concentrated chiefly in the sternum ribs, flat bones of the skull and the proximal ends of the femur and humerus. Normally, red cell production by the marrow in these areas just balances the physiologic destruction or loss of red cells. The abnormal loss of red cells is met by a corresponding increase in production. The bone marrow scarcely can be expected to meet the demands made upon it unless it is adequately supplied with iron plus additional nutritive elements essential for red cell and hemoglobin manufacture.

FOLARMOUR is a logical therapy for secondary anemia based on a present day concept. Folarmour capsules combine in one formula all the known factors necessary for hemopoiesis. Two capsules daily supply:

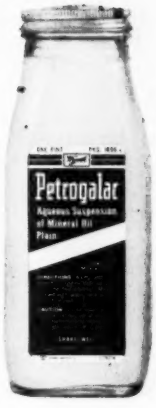
Ferrous Sulfate (exsiccated)	332 mg.
Liver Extract Concentrate (secondary fraction)	500 mg.
Folic Acid	10 mg.
Thiamine Hydrochloride	10 mg.
Riboflavin	20 mg.
Pyridoxine Hydrochloride	0.2 mg.
Nicotinamide	150 mg.
Calcium Pantothenate	5 mg.
Ascorbic Acid	150 mg.
Vitamin A	25,000 U.S.P. Units
Vitamin D	1,000 U.S.P. Units

have confidence in the preparation you prescribe — specify "ARMOUR"

ARMOUR *Laboratories*

HEADQUARTERS FOR MEDICINALS OF ANIMAL ORIGIN • CHICAGO 9, ILLINOIS

HABIT TIME OF BOWEL MOVEMENT



SAFE . . .

PETROGALAR, given at bedtime—not with meals—has no adverse effect on absorption of nutritive elements. It provides a relatively small but highly effective dose of mineral oil augmented by a bland, hydrophilic colloid base. The result is a soft-formed, easily passed stool, permitting comfortable bowel movement.

If preferred, PETROGALAR may be given thinned with water, milk, or fruit juices—with which it mixes readily.

Wyeth

Wyeth Incorporated, Phila. 3, Pa.

THE

velvety softness

THAT IS KIND TO THE BOWEL

In the treatment of constipation, Kondremul contributes a velvety soft colloidal emulsion of microscopically fine particles which mix intimately with the dry fecal residue—easing elimination and encouraging regular bowel habits.

To meet various types of constipation, Kondremul is supplied in three forms:

KONDREMUL Plain (containing 55% mineral oil)

KONDREMUL with non-bitter Extract of Cascara (4.42 Gm. per 100 cc.)

KONDREMUL with Phenolphthalein—.13 Gm.(2.2 grs.) phenolphthalein per tablespoonful

KONDREMUL

...an emulsion of Mineral Oil and Irish Moss

THE E. L. PATCH COMPANY
STONEHAM, MASS.

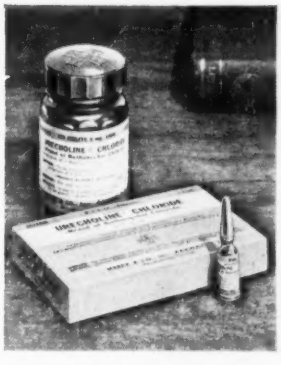
To Prevent or Control Postoperative Urinary Retention

Bladder Atony

Intestinal Atony

Urecholine® Chloride provides the much-desired answer to the distressing problem of urinary retention. It may be employed as an effective means of *prevention*, by routine administration following abdominal surgical procedures. Equally effective when used for *treatment*, Urecholine affords prompt relief and obviates, in a large percentage of cases, the necessity and inconvenience of catheterization. Reproducing the effects of parasympathetic stimulation, the drug is effective also in the treatment of *chronic* or functional urinary retention, when due to muscular atony without obstruction.

Urecholine Chloride has been found equally beneficial in the prevention and relief of postoperative abdominal distention, in gastric retention following vagotomy, and in selected cases of megacolon.



Supplied as 5 mg. tablets in bottles of 100 for oral use, and in cartons of six 1 cc. ampuls, 5 mg. per cc., for subcutaneous injection.

Literature concerning Urecholine Chloride is available upon request

MERCK & CO., Inc.
Manufacturing Chemists
RAHWAY, NEW JERSEY

MERCK

Urecholine® Chloride

(Brand of Bethanechol Chloride)
(Urethane of β-Methylcholine Chloride Merck)

PRODUCTION OF CANS UP 14 PER CENT IN FIRST SIX MONTHS

New York.—The Manufacture of cans for food and other products increased by more than one and one-half billion units, or about 14 per cent, during the first half of 1950 over the comparable period a year ago, L. W. Graaskamp, vice-president in charge of sales for the American Can Company, reported here today.

Graaskamp stated that estimated production for the period was the equivalent of approximately 12,880,000,000 No. 2 cans. The figure for the same period in 1949 stood at about 11,300,000,000, he said.

The increase in the output of food containers, Graaskamp continued, was over 500,000,000 units — from about 7,354,300,300 during the first half of 1949 to approximately 7,860,000,000 this year. The biggest single volume increase in food cans was recorded for fruit and vegetable containers, including juice cans, which rose from about 2,725,000,000 during the first six months of 1949 to 3,090,000,000 for the same period this year, he said.

Can production for non-food products showed a rise of almost 27 per cent—from approximately 3,958,000,000 in 1949 to approximately 5,020,000,000 this year, he added.

CORAMINE

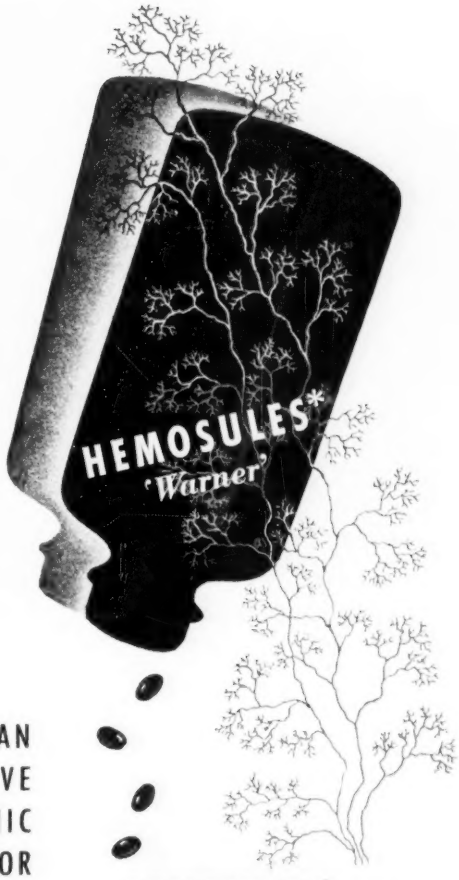
An announcement has been made that Coramine will now be available in 20 cc. multiple dose vials. Ciba Pharmaceutical Products, Inc. is issuing this new, large economical vial because in certain conditions Coramine is now being administered in much larger doses than heretofore.

In shock and barbiturate poisoning, for example, excellent results have been reported from the administration of 5 to 10 cc. of Coramine every 10 minutes. The new 20 cc. vial with rubber diaphragm closure will facilitate the administration of Coramine in these large doses.

INDEX TO ADVERTISERS

THE EFFECTIVE HEMATINIC FOR THE ANEMIAS OF . . .

nutritional inadequacies
pre- and post-natal demands
dietary restrictions
gynecological disorders
acute or chronic blood losses
pre- and post-surgical conditions
acute or chronic infections
debilitating diseases
"run-down" or lowered resistance states



AN EFFECTIVE HEMATINIC FOR ALL HYPOCHROMIC ANEMIAS..... HEMOSULES* 'Warner'

The recommended daily dose of 6 HEMOSULES* provides...

15 grains of dried Ferrous Sulfate, U.S.P., equivalent to 285 mg. of assimilable iron or 28 x M.D.R.†		
Thiamin hydrochloride (Vitamin B_1)		6.0 mg. (6 x M.D.R.†)
Riboflavin (Vitamin B_2)		6.0 mg. (3 x M.D.R.†)
Ascorbic acid (Vitamin C)		90.0 mg. (3 x M.D.R.†)
Niacinamide**		24.0 mg.
Pyridoxine hydrochloride (Vitamin B_6)***		3.0 mg.
d-Panthenol (equiv. to 3.0 mg. Pantothenic acid)***		2.82 mg.
Folic acid***		1.2 mg.
Liver Fraction 2	(15 grs.)	972.0 mg.

*Trade Mark

†Minimum daily adult requirement.

**The minimum daily requirement for niacinamide has not been established.

***The need for pyridoxine hydrochloride, pantothenic acid and folic acid in human nutrition has not been established.

WILLIAM R. WARNER
Division of Warner-Hudnut, Inc.
New York • Los Angeles • St. Louis

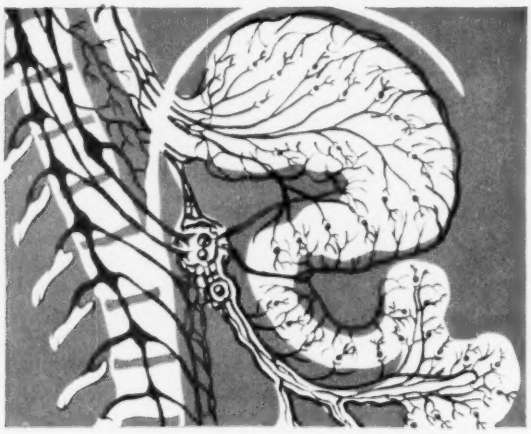
BANTHĪNE*

BROMIDE

BRAND OF METHANTHELINE BROMIDE

Treatment individualized to patient.

One or two tablets (50 or 100 mg.) every six hours, around the clock, in peptic ulcer management.



THE NEUROGENIC APPROACH— A MAJOR ADVANCE IN ULCER THERAPY

BANTHĪNE is not an alkali. It is a true anticholinergic drug which, through its inhibition of excess vagal stimulation, controls hypermotility consistently, reduces hyperacidity in most instances and relieves ulcer pain promptly.

The clinical success of BANTHĪNE has been demonstrated by roentgenographic and gastroscopic evidence of healing as well as by laboratory and symptomatic evidence of improvement.

**Trademark of G. D. Searle & Co., Chicago 80, Illinois*

SEARLE

RESEARCH IN THE SERVICE OF MEDICINE